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Alternans: Report of a Case Associated with Acute Pericarditis

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Alternans is a regularly recurring change in the metabolism of the myocardium resulting in a regular variation in each second heart contraction. The beats are regular or almost regular in time. The regularly recurring changes in the heart beat may be accompanied by equally regular, slight, alternating changes in the diastolic periods. Because of its repetitious character alternans belongs to the allo- or regular rhythms rather than to the arrhythmias.

Alternans may involve the auricles, ventricles, or strips of myocardium. It may manifest itself mechanically or electrically. The alternation may be quantitative, expressed as weak and strong beats. It may show itself qualitatively by other changes in the heart contractions or by recorded effects of the accompanying, representative changes in the heart muscle.

Mechanical alternans may be felt, seen, or heard as "arterial" (pulsus) alternans in the peripheral arteries or as "cardiac" alternans at the apex. It may also be seen in the heart through the fluoroscope, in the capillaries with the microscope, or directly in an exposed, experimental heart. It may be recorded with a sphygmograph or cardiograph. It is most frequently recognized by the alternately strong and weak beats heard over the brachial artery while estimating the blood pressure with the sphygmomanometer. The pulse speed heard below the sphygmomanometer cuff is twice as frequent at low pressures as at high cuff pressures. The heart component of mechanical alternans is a function of the left ventricle only.

Alternation recognizable at the heart (cardiac alternans) may not be detected at the wrist (arterial, pulsus alternans). The signs of mechanical alternans are usually not reflected in the electrocardiogram.[1] Alternans can be recognized in the empty heart. The apparently dead, noncontracting heart or myocardial strips may yield electrocardiographic tracings showing electrical alternans.

Traube separated alternans from bigeminy in 1872. It is distinguished from pseudoalternans or bigeminy by the equal or almost regular timing of the alternans contractions as contrasted with the long and short pauses in bigeminy. The pauses between the contractions in alternans need not be absolutely equal. Frequently the interval following the strongest beat or, in bidirectional electrical alternans, the upright deflection, is followed by a slightly longer pause. The gross difference in the pauses characterizing bigeminy is not approached in alternans. Electrocardiographic evidence may be needed to distinguish alternans from bigeminy. Alternans and bigeminy can coexist, every other contraction of sinus origin being smaller than its sinus-originated predecessor.[2]

In electrical alternation every other R and S wave or even every other Q wave may vary in height or depth but in a regular way. The complexes may alternate in amplitude, form, or direction or the alternating complexes may differ in all the ways possible in amplitude, form, and direction. Alternation may affect any part of the complex but never all parts of the complex simultaneously. In other words, an electrocardiographic record has not been observed with alternation in both its auricular and ventricular components.

Electrical alternans usually is manifested by alternation in the height of the R wave. Slight differences (alternans parvus) are commoner than great differences. Electrical alternans shows itself not uncommonly as a regular variation in

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the height of the T waves especially in Lead I. Qualitative, alternating changes may be recognized in the P wave or in ventricular complexes as variations in form or direction. Bidirectional electrical alternans is characterized by complexes alternating in direction.

Regular alternation of upward and downward deflections in the electrocardiogram is the least common type of alternans. It has been observed in patients with ventricular tachycardia who had been treated with digitalis.[3-8] The directional alternation in these cases was accompanied by a time alternation in the intervals between the complexes. The complex with the upright component was usually followed by a time interval longer than that following the complex with the downward component. Braun and Wosicka's patient developed bidirectional alternans and ventricular tachycardia after the use of digitalis purpurea but recovered on digitalis lanata.[9]

Mechanical alternans and electrical alternans are usually not found simultaneously. According to the French (Poumailloux, Laubry) and Italian (Chini, Condorelli) authors, their coexistence is purely coincidental. The French and Italian authorities even gave prognostic importance to the distinction between mechanical and electrical alternans. They regarded mechanical alternans gravely while regarding electrical alternans lightly. There is no clinical evidence of electrical alternans being less serious than mechanical alternans. Kisch holds alternans manifested mechanically or registered electrically as indicating essentially identical heart changes.[10]

Alternans is most frequently encountered clinically in patients 40 to 60 years of age with arterial hypertension and arteriosclerosis.[11] It is also found in association with failure of the left ventricle, in acute infections, in patients treated with digitalis, and less commonly in vascular lues. In a case described by Katz and Hamburger there were metastatic carcinoma nodules in the heart.[12] Alternans is a presumptive sign of severe anatomic changes in the myocardium.

Conditions favorable to the production of alternans create an alternans "disposition" or alternans latency. Alternans may cease but the "disposition" to its return remains. Many such conditions can be grouped under myocardial weakness. In particular they interfere with recovery following systole. Malnutrition of the myocardium resulting from reduction in the quantity or quality of blood flowing in the capillaries can be the predisposing factor. According to Lewis, a heart showing alternans always has an organic lesion.

It is significant that alternans is most frequently seen in tachycardia, especially ventricular tachycardia and in paroxysmal tachycardia associated with coronary insufficiency. It is also encountered in auricular flutter, another example of marked tachycardia. Tachycardia hinders recovery after myocardial contraction.

An explanation applicable to all types of alternans has not been formulated.[13-15]

Separate ectopic foci, alternating right and left bundle-branch block, parasystole, re-entry, and circus movement have been advanced as possible mechanisms for bidirectional electrical alternans.

Alternans has usually been regarded as an unfavorable omen. When it was first recognized it was always found in gross cardiac disease. Ventricular tachycardia, one of the conditions most frequently complicated by alternans, is itself a serious occurrence. Most of the reported cases of bidirectional alternans had serious heart disease and soon died. Lewis has estimated the probable duration of life in the average patient with alternans as varying from two months to two years. Mackenzie reported a patient showing alternans for fourteen years.

In general, the more persistent the alternans the worse the outlook. Awareness has led to more frequent detection of alternans and in reversible conditions. The outlook depends wholly upon the underlying myocardial injury. Associated with a curable condition such as an acute infection, especially in a youthful patient with normal coronary arteries, alternans has a much more favorable outlook than in the usually elderly alternans patient with arterial hypertension and arteriosclerosis. Slight alternation can be as serious as an easily detectable example.

CASE REPORT

A 16-year-old boy entered the West Suburban Hospital April 27, 1945. He was an athlete and had been well up to two weeks before admission. He had not had rheumatic fever nor frequent sore throats. Numerous physical examinations had always yielded normal findings.

Two weeks before admission to the hospital he experienced severe tightening across the front of his chest and palpitation while sitting quietly following an after-

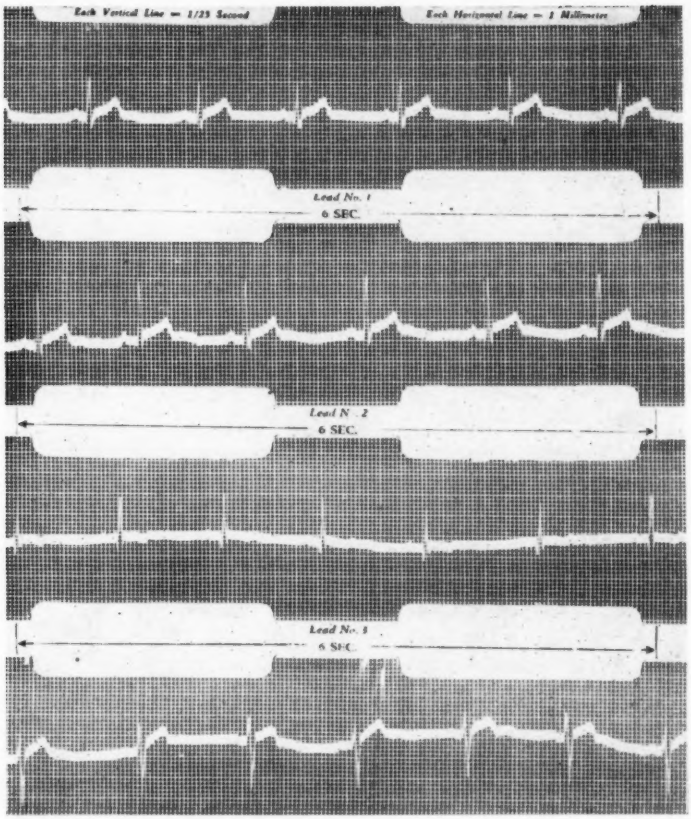

FIGURE 1. At onset. April 20, 1945. Elevated $ST_{1,2,3}CF_4$.

noon of competitive athletics. He became dyspneic and within a few hours orthopneic. After three days in bed he returned to school feeling weak. His temperature never exceeded 98° F. but his pulse was constantly about 100. He complained of pain in both shoulders, especially the left. He had pain in the upper abdomen and vomited. He fainted twice. One week before hospitalization an x-ray of his chest showed "a large heart shadow." The electrocardiogram at that time showed a regular sinus mechanism, the rate was 60, PR was 0.12 second. ST was elevated in Leads I and II and CF_4 (Figure 1).

The patient was athletic in stature and well-nourished. On admission to the hospital his temperature was 98° F., pulse 120, and respirations 30; his blood pressure was 122/70. His general pallor contrasted with his flushed cheeks. His pupils were dilated. The neck veins were engorged. The pulse was rapid, regular, of small volume and varied paradoxically with respiration.

Alternation was not detected by palpation of the radial pulse nor by examination of the heart. The apical impulse could not be defined although a faint pulsation was felt in the precordium. The left border reached the mid-axillary line, the upper border the second rib, and the right border the right edge of the sternum. The cardiohepatic angle was obscured. The heart sounds were normal but muffled. Pericardial friction was not heard.

The lungs were clear, the bases moved normally, and Bamberger's sign was absent. The liver was felt three fingers below the ribs. The abdominal flanks were dull. The legs were cyanotic and the foot arteries could not be felt. The urine contained a trace of albumin and a few hyaline casts. Hemoglobin was 90 per cent; red blood cells 5,000. White blood cells numbered 13,850, with 58 per cent polys, 40 per cent lymphocytes, and 2 per cent eosinophils. The sedimentation rate was 9 mm. per hour. The blood count was unchanged during his hospital stay except for a recession of the leukocytes to 7,700. The serum protein was 6.5 gm.; the albumin-globulin ratio was 3/2. The cephalin flocculation was positive.

Agglutination tests for typhoid, paratyphoid A and B, typhus and brucellosis gave negative results. The intradermal injection of 0.1 mg. of Old Tuberculin produced no reaction.

THE admission electrocardiogram showed a regular sinus mechanism. The rate was 105 (Figure 2). The maximal deflections alternated in direction in Leads I and CR_4. This abnormality was indicated less

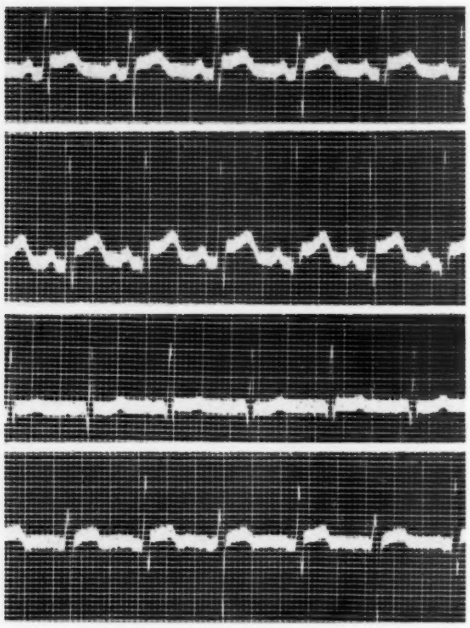

FIGURE 2. April 27, 1945. R and S waves of alternating amplitude. Elevated $ST_{1,2}$, CR_1.

strikingly by an alternation in depth of S waves in Leads II and III. The time interval between the complexes was equal. $ST_{1,2}$ and CR_1 were elevated. Each alternate complex in Lead III had a somewhat deeper Q wave and a slightly less elevated R spike. The maximum deflections from the isoelectric line were equal in amplitude. The time interval following the negative deflection was the same as that after the positive deflection. The complexes had normal contours. Deformities characterizing bundle-branch block, such as widened QRS and T wave directed in opposite direction to the principal deflection, were lacking. Electrocardiograms showed the bidirectional alternans persisting forty-eight hours after its discovery.

Traces of the alternation were found for three weeks. T waves became progressively more flat. The ST segments of the limb leads lowered. The negativity of T wave in the fourth lead increased. Fluoroscopic and x-ray examinations showed the cardiac shadow greatly enlarged. The left border pulsated slightly. The roentgenologist's interpretation was cardiac hypertrophy.

The temperature rose to 100° F. and remained at this level during the third and fourth weeks of his hospital stay. The blood pressure remained unaltered.

A needle was introduced in the fifth left intercostal space next to the sternum two days after admission. The bloody fluid aspirated was thought to come from the right auricle. Aspiration in the same area two weeks later gave the same result.

Fluid gathered in both pleural sacs. Clear, straw-colored fluid aspirated through the eighth interspace in the left midscapular line on May 13 had a specific gravity of 1.009 and lymphocytes as the predominating cells. No bacteria were found in smears or cultures. A guinea pig injected with the fluid did not develop tuberculosis.

Dyspnea increased. The spleen became palpable. A massive soft-pitting edema developed in the feet. A study of the sternal marrow showed only the changes due to infection.

On May 29, four weeks after admission, 1,500 cc. of pink fluid was aspirated from the right pleura relieving the orthopnea. A cervical lymph gland showed only chronic, nonspecific inflammation. On May 31 aspiration in the fifth interspace in the anterior axillary line yielded 300 cc. of bloody fluid similar to that of the two previous taps at the left of the sternum. This time, however, the needle was felt scratching against the ventricular wall, proving that the bloody fluid was in reality pericardial exudate. This bloody fluid did not clot. The predominating cells were erythrocytes and lymphocytes. This serosanguinous fluid did not produce tuberculosis in a guinea pig. Cultures of the fluid yielded no growth.

The patient improved rapidly after the last pericardial aspiration. His temperature became normal. Convalescence was rapid. The fluid in the pleurae, the peritoneum, and under the skin disappeared. The liver enlargement subsided. The spleen remained palpable for several weeks. No heart murmurs were ever heard.

The patient has not had any subsequent illness. He has maintained his full scholastic schedule and won honors throwing the discus. Subsequent electrocardiograms show only slight elevation of ST in all three standard leads and in CF_4 (Figures 3 and 4).

Fluoroscopically the heart is normal in size and shape. Its borders move amply during systole and diastole. The heart shifts in the thorax with change of position. No murmurs or abnormally accentuated sounds have ever been heard. The sedimentation time is normal. The Mantoux test remains negative.

DISCUSSION

This patient probably had acute nonspecific pericarditis accompanied by inflammation of the adjacent serous sacs and also by electrical alternans.

The first tracings obtained show the classical elevation of the RS-T segments with a dome-shaped T. There is no depression of RS-T segment in any lead at any time and the T waves in Leads I and III are not reciprocally related. These are the essentials of the electrocardiographically diagnostic pattern of pericarditis.[16]

The electrocardiographic changes due to pericarditis with effusion have been extensively discussed.[17-23] The important changes which may develop in the course of pericarditis with effusion are lowering voltage, elevation of the RS-T interval, and inversion of the T waves. These electrocardiographic signs of pericarditis have been demonstrated to be due to subepicardial myocarditis.

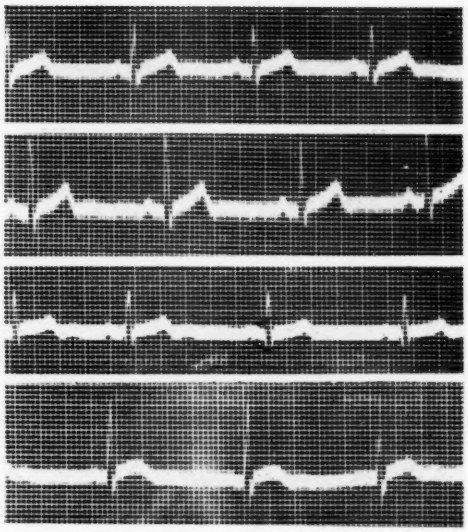

FIGURE 3. September 3, 1946. Moderately elevated $ST_{1,2,3}CF_4$.

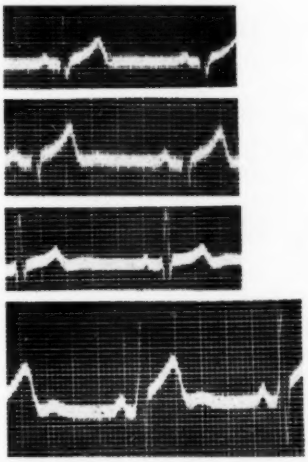

FIGURE 4. December 29, 1947. Elevated $ST_{1,2,3}CF_4$.

I have been unable to find any instance of bidirectional alternation occurring in acute pericarditis. Bidirectional electrical alternans with a sinus mechanism is at least unusual. Tachycardia is almost always present when electrical alternans is a feature. The tachycardia in my patient was only moderate (90 to 105).

A POSSIBLE explanation of the bidirectional alternans in my patient would be a partial block in Tawara's node or in the bundles. The tissue injured by infection would seem to require twice the normal time for recovery of its conductivity. The stimulus arising in the sinus node would go down the branch which had regained its conductibility while the other branch was passing through its twice-normal refractory period. This is equivalent to saying that we are dealing with an alternating bundle-branch block.

Digitalis had not been given to my patient. He had never used tobacco. The alternans was the only finding interpretable as evidence of myocardial disease except that myocarditis is regarded as invariably present in pericarditis. The swollen liver and ankles were explained by the interference with the return flow to the heart offered by the tamponade effect of the pericardial exudate. The pleural and peritoneal effusions also obstructed the venous flow.

Coronary thrombosis can not be excluded as a possible diagnosis.

Helpful advice in preparing this paper has been given by Dr. L. N. Katz and Dr. J. Bailey Carter.

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Intravenous Procaine

AN EVALUATION OF SOME OF ITS USES

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Until recently, procaine hydrochloride was considered by most physicians only as a local anesthetic. Intravenous injection was considered dangerous.

However, in 1937 Lewey[1] reported on the administration of procaine intravenously in cases of tinnitus aurium with no untoward reactions. More recently, the drug has been given by the intravenous route for a variety of unrelated ailments, and it has even been used as a general anesthetic in obstetrics and in general surgery.[1-7, 11, 14-17, 19, 20, 25]

In this paper we shall present an evaluation of some of these uses of intravenous procaine and correlate the experiences of others with our experiences over a period of eighteen months.

CHEMICAL PROPERTIES, DETOXIFICATION, AND EXCRETION

Procaine hydrochloride, B-diethylaminoethyl p-aminobenzoate hydrochloride, is similar in structure to benadryl (B-dimethylamino-ethylbenzohydryl ether hydrochloride) and to acetylcholine (Figure 1).

Heat stable (100° C.) and easily soluble in water, procaine is quickly hydrolyzed (52 per cent within five minutes) to form p-aminobenzoic acid and diethylaminoethanol. The former is acetylated and 94 per cent is excreted in the urine within twenty-four hours. The fate of the latter is unknown.[10]

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ACTIONS

Graubard, et al.[14-17] and State and Wangensteen[25] have described the actions of procaine as follows: (1) antihistaminic; (2) anti-acetylcholine (nerve-blocking); (3) direct action on cells (especially nerve and endothelial cells), and (4) epinephrine-potentiating action.

The exact mechanism of action of the antihistaminic drugs is unknown at present but their local anesthetic effect is well known. The anti-acetylcholine effect is said to be a curare-like phenomenon, both sensory and motor synapses being affected. This is the basis for the use of local or intravenous injection of procaine in causalgias where an antidromic reflex is the apparent cause of the pain-vasospasm-muscle spasm cycle. The afferent and efferent stimuli are blocked by the procaine and the cycle is broken[8, 17, 20, 25] (Figure 2). Direct effects on nerve cells may cause some of the toxic manifestations as well as result in breaking the vicious cycle of antidromic reflexes. The potentiation of the action of epinephrine is the rationale for the use of procaine in asthma.[7] This property may be the true reason for some reactions thought to be due to procaine.[4, 22]

TOXICITY AND DOSAGE

In experimental animals toxic symptoms occur on rapid injection of procaine intravenously in doses exceeding 20 mg. per kilogram of body weight or when a blood level of 25 mg. per 100 cc. is exceeded.[10] Ascorbic acid deficiency decreases and administration of ascorbic acid and glucose, or both, increases the toxic dose.[22] The

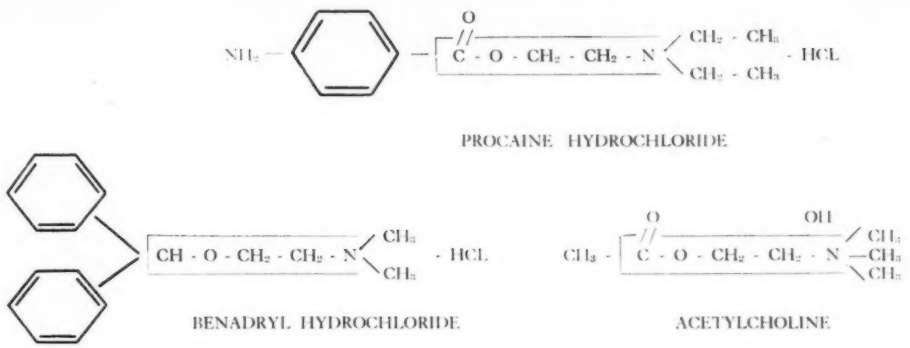

FIGURE 1. Structural formulas show a close chemical relationship between procaine, benadryl and acetylcholine.

ability of the barbiturates to abort or to prevent convulsions is well known.

At least 90 per cent of the procaine disappears from the blood stream within twenty minutes after injection, due to rapid hydrolysis of the procaine and to its rapid diffusion into the body fluids.[3] Graubard, et al.[12] concluded that the maximum safe dose is that amount which can be excreted or detoxified within twenty minutes after injection. Clinically they found that the minimum effective dose was 4 mg. per kilogram injected in twenty minutes. They referred to this as "the procaine unit" and described a "rotameter" to be used for measuring this dose accurately.[13]

With this dosage they observed the following "undesirable reactions" in a series of 2,000 injections: marked dizziness, apprehension, sensations of trembling, sleepiness, and temporary unconsciousness.

Our series of 271 injections of procaine intravenously included: 112 injections of 275 to 1,500 cc. of 0.1 per cent solution; 51 injections of 500 to 800 cc. of 0.1 to 0.13 per cent solution; 100 injections of 500 cc. of 0.13 per cent solution; 1 injection of 500 cc. of 0.2 per cent solution; and 3 injections of 300 to 1,500 cc. of 1 per cent solution. It was our impression that the objective and subjective complaints of the patients paralleled the concentration of the solution, the rate of injection, and the nervous stability of the patients. No instance of sensitivity reaction or convulsions was observed.

Tremors were noted in 2 patients: (1) A 46-year-old man with excruciating lightning pains due to taboparesis, consistently developed marked tremors of the upper and lower extremities. These subsided within a few minutes after the injection was stopped and were not prevented by administration of SECONAL 0.1 gm. before one injection. (2) A man aged 54 years, with chronic urticaria, developed generalized tremors but stated that they caused him no discomfort. He had been taking an elimination diet a week previously and may have been deficient in ascorbic acid, although generally well nourished.

Nausea was noted by 3 patients: (1) A 59-year-old neurotic woman complained of nausea and faintness when her systolic blood pressure fell 30 mm. of mercury. The symptoms vanished when the rate of injection was decreased. (2) An asthenic, neurotic, 32-year-old woman with ulcerative colitis complained of nausea on two occasions and vomited once following an injection of 500 cc. of 0.1 per cent procaine. (3) A 76-year-old woman with destructive arthritis of both hips and hypertensive cardiovascular disease with auricular fibrillation suddenly vomited after 300 cc. of 0.13 per cent solution had been given. Her blood pressure rose from 186/108 to 224/132 and her pulse from 100 to 140 per minute. She experienced no reaction on 5 subsequent injections. All of these individuals were of psychoneurotic makeup and this may have been a factor in the causation of the nausea and vomiting.

One 56-year-old man with severe degenerative and rheumatoid arthritis developed a shaking chill after he had returned home after his third injection. He was admitted to the hospital four hours later and died, apparently of a myocardial infarction, shortly thereafter. An autopsy was not obtained. Tests for pyrogens with samples from the same batch of procaine, performed on 3 rabbits with stable temperatures for five days, and also on a human volunteer, were negative. It is unlikely that the procaine *per se* was related to this man's death.

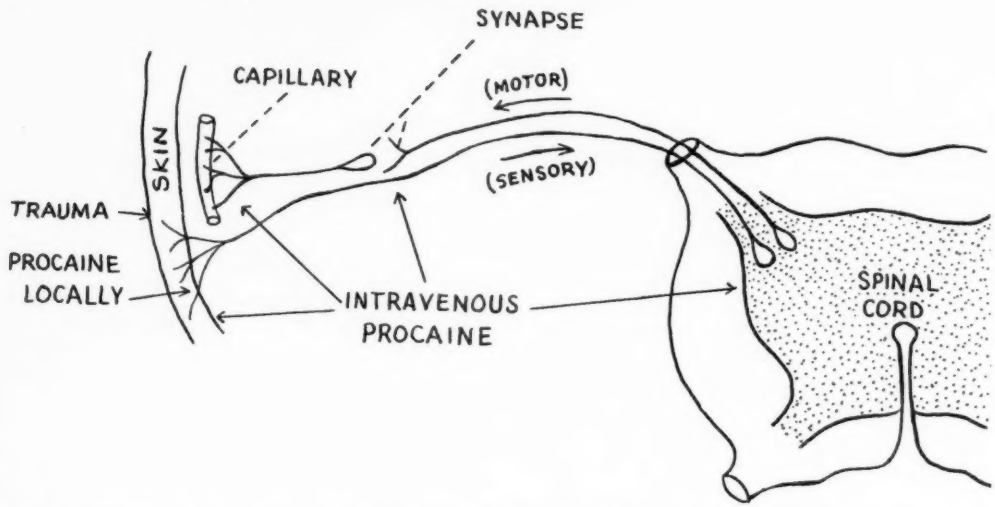

FIGURE 2. Interruption of the antidromic reflex occurs at four points following the intravenous injection of procaine (schematic).

CLINICAL USES

At the Guthrie Clinic and the Robert Packer Hospital, procaine has been given intravenously for the general conditions listed in Table 1.

TABLE 1

INTRAVENOUS PROCAINE AS USED AT THE GUTHRIE CLINIC AND ROBERT PACKER HOSPITAL FOR EIGHTEEN MONTHS (1947 TO 1949)

CONDITION TREATED	NUMBER OF PATIENTS	NUMBER OF INJECTIONS
Jaundice	1	3
Arthritis	15	123
Osteoarthritis	10	74
Rheumatoid	5	49
Fracture	1	13
Postoperative pain	12	14
"Neuralgias"	12	82
Herniated disks	5	13
Tabes dorsalis	4	44
Miscellaneous	3	25
Allergic states	13	29
Serum reactions	5	8
Penicillin reactions	2	4
Miscellaneous	6	17
General anesthesia*	4	4
Cardiac arrhythmia	3	3
TOTAL	61	271

*Given in 1945 by Dr. W. E. Dotter.

Jaundice—Three injections of 1,500 cc. of 0.1 per cent procaine were given intravenously to a 74-year-old woman with intractable generalized pruritus due to a progressive jaundice, presumably caused by carcinoma of the head of the pancreas. There were no reactions and the pruritus ceased during the injections but recurred shortly afterwards. Pyribenzamine orally seemed to be equally effective.

Lundy[19] recommended the use of intravenous procaine for temporary relief of the intractable pruritus which sometimes accompanies jaundice. If the patient is receiving glucose or saline intravenously, addition of procaine to a concentration of 0.1 to 0.2 per cent may give considerable temporary relief.

Arthritis—Fifteen patients with arthritis received an average of 8.2 injections each of 275 to 500 cc. of 0.1 to 0.2 per cent procaine over a period of two days to six months. At first measured doses were given as recommended by Graubard, et al. However, since Allen [1,2] used up to 13 cc. of 1 per cent procaine per minute, we used, in most of our cases, a standard dose of 500 cc. of 0.1 per cent solution as an initial dose. Subsequent doses were 500 cc. of 0.1 to 0.2 per cent solution (a total of 0.5 to 1 gm. of procaine), depending upon the subjective complaints of the individual patients. Reactions were minimal except in 1 case (described above) in which the patient died after a severe chill and possibly a myocardial infarction six hours after his third injection.

The results of treatment were, unlike Graubard's cases, not spectacular. In general there appeared to be some decrease in stiffness and pain and in 1 or 2 cases improvement was rather striking. However, such striking improvement was inconstant, even in the same patient. For example:

Patient 2 in the group with osteoarthritis (Table 2) arrived by taxi for his eighth treatment and felt

0—No relief
+—Slight relief
++—Marked relief
+++—Cured

TABLE 2

RESULTS IN THE TREATMENT OF OSTEOARTHRITIS (11 CASES) WITH INTRAVENOUS PROCAINE

Patient	Age	Sex	Duration (Years)	Description of Complaints	Number of Treatments	Dosage		Duration of Treatments	Side Reactions	Results		
						Per Cent	Cubic Centimeters			Immediate		Final
										Degree	Duration	
1	59	F	3	Moderate generalized pains, few joint changes	9	0.1	275 to 300	2 weeks	Dizziness, nausea, B.P. fell 30 mm. once	+ to++	2 to 24 hours	A little less pain, no objective change
2	59	M	2	Very severe, disabling; large, hypertrophic joints	10	0.1	300 to 500	3 weeks	0	+ to ++	8 hours to 5 days	A little less pain on walking; no objective change
3	70	F	10	Moderate; severe osteoporosis of spine	4	0.1	300 to 500	6 days	0	0 to +	6 to 8 hours	No improvement
4	68	F	20	Severe changes both knees, fractured left hip	6	0.1	350	8 days	0	± to +		R.O.M. increased 10 per cent (left knee)
5	73	M	25	Severe, disabling, right hip; neurectomy no help	22	0.1 to 0.13	500	5 months	0	0 to ++		Less pain, R.O.M. slightly increased
6	64	M	5	Moderate pain in right knee kept him in bed	10	0.1	500	10 days	0	0 to ++	6 to 24 hours	Walks almost normally, only slight limp
7	84	M	?	Bedridden, deformed left knee	3	0.1	500	3 days	0	?	?	Too deteriorated to help or evaluate
8	74	F	10	Mild, generalized; severe radicular pains	21	0.1 to 0.13	500	5 months	0	0		Patient thought it helped "a little"—no change
9	56	M	20	Severe, disabling, mixed	3	0.13	500	3 days	Chill 30 min. after 3rd	0		Died six hours after chill
10	60	M	5	Vague backaches	2	0.1	500	2 days	0	0		Didn't like needles
11	75	F	3	Destructive, both hips, severe aching pains	7	0.13	500	8 days	Chill with 4th, vomited with first	0		Very little pain two weeks later

so well immediately following the treatment that he walked home. This was an exceptional instance. He obtained very little relief with the ninth and tenth injections and then discontinued the treatments. One year later he was confined to bed because of the arthritis and a few months later was reported much improved after drinking a special home-brewed wine.

Another "spectacular result" occurred in patient 5 in the group with rheumatoid arthritis (Table 3):

Patient 5 represented a case of moderate, acute rheumatoid arthritis in a 32-year-old lady with an exacerbation of chronic ulcerative colitis. She received eight injections of 500 cc. of 0.1 to 0.13 per cent procaine within eleven days. During this time she also received sulfathalidine 3 gm. every six hours. Both the colitis and the arthritis subsided in that time and the patient had very slight residual joint changes with no impairment of the range of motion. However, she had made a similar rapid recovery from an episode a few months earlier without benefit of procaine.

Of the 7 patients with osteoarthritis who received more than the initial course of five consecutive daily injections, 5 of the patients noticed immediate or gradual improvement. However, none of the 6 patients followed for one month or longer showed permanent improvement. Most said they were the same or slightly better (Table 2).

Of the 6 patients with rheumatoid arthritis only 2 said they had less pain and only 1 showed any objective evidence of improvement. Patient 6 had an associated severe fracture of the left knee and the range of painless motion increased, after 13 injections over a period of twenty days, from 10 per cent to 60 per cent (Table 3).

GRAUBARD, et al.[12-14,16] and Allen, et al.,[2] as well as other authors, reported good results in the treatment of osteoarthritis with intravenous procaine but little benefit in the treatment of rheumatoid arthritis.

The etiology of osteoarthritis has been described[25,26] as (1) trauma, (2) arteriosclerosis (present in only 58 per cent of cases), (3) infection (although no lymphocytic or polymorphonuclear infiltration is demonstrable), and (4) endocrine disturbances. With the advent of Hench's work with cortisone the last seems to have assumed increased importance.

It is obvious that, in diseases such as osteoarthritis where the process is continuous, injection of procaine does not remove the cause; but it may relieve the spasm and pain, at least temporarily.

In acute rheumatoid arthritis, such as afflicted patient 5, there may have been an allergic element which was suppressed by the antihistaminic effects of procaine; but in cases of far advanced, chronic rheumatoid arthritis, irreversible atrophic and fibrotic changes have taken place and improvement would be unexpected. Graubard, et al.[17] point out that this is also true of the reflex sympathetic dystrophies. (No cases of the latter condition were included in our series but the rationale for the use of procaine intravenously early in such cases seems clear from Graubard's work.)

Postoperative pain—Procaine intravenously to allay postoperative pain has been used with good results and no ill effect by McLachlin,[20] Graubard, et al.[14] and others. These authors noted that relief from pain continued only during or shortly following the administration of 0.1 per cent solution but that during that time no morphine or other depressant drug was required. The rationale is again based on the fact that high concentrations of procaine occur in traumatized tissues.

We also have observed no untoward effects and considerable analgesia in 12 patients receiving 0.1 per cent procaine in routine postoperative infusions. Good results were obtained in cases following spinal fusion in which considerable pain usually is expected.

"Neuralgias"—Various painful neurologic conditions were treated with intravenous procaine as follows:

- 5 patients with pain one month to three years after laminectomy for herniated intervertebral disk received 13 injections of 0.1 per cent procaine;
- 4 patients with lightning pains of tabes dorsalis for four to twenty years received 44 injections of 0.13 per cent procaine;
- 1 patient with "possible multiple sclerosis" and painful cramps in the right leg received three injections of 0.13 per cent procaine;
- 1 patient with osteoarthritis and severe radicular pains in the right subscapular region received 21 injections of 0.1 to 0.13 per cent procaine;
- 1 patient with moderate pain due to postherpetic neuritis received one injection of 0.1 per cent procaine.

Not one of these patients showed any permanent improvement which could be ascribed to the effect of the procaine and most had little relief of acute pain during or shortly following the injection. The patient with the severe radicular pains received within an hour 1,500 cc. of 0.1 per cent procaine and within a few minutes thereafter required 100 mg. of DEMEROL for relief of pain. However, 3 of

•—The fractured knee
0—No relief
+—Slight relief
++—Marked relief
+++—Cured

TABLE 3

RESULTS IN THE TREATMENT OF RHEUMATOID ARTHRITIS (6 CASES) WITH INTRAVENOUS PROCAINE

Patient	Age	Sex	Duration (Years)	Description of Complaints	Number of Treatments	Dosage		Duration of Treatments	Side Reactions	Results		
						Per Cent	Cubic Centimeters			Immediate		Final
										Degree	Duration	
1	50	M	7	Severe, generalized, inactive; deformities	13	0.1	500	28 days		+ to +	6 to 24 hours	No improvement
2	75	F	20	Severe nocturnal pains, moderate deformity	7	0.1	500 to 700	7 days		0 to +	4 to 24 hours	A little less pain; no definite change
3	45	M	3	Severe Marie-Strümpell's; cardiac decompensation	14	0.1	500	32 days		0 to ++	4 hours to 7 days	Less pain; no objective change
4	54	M	20	Severe, generalized, deforming; epileptic	7	0.1	300 to 500	11 days	Sweat, apprehension, clonic movements once	0 to +		No help
5	32	F	½	Acute, mild changes; ulcerative colitis	8	0.1 to 0.13	500	11 days	Faintness, nausea, vomited once	0 to ++	2 to 24 hours	Arthritis and colitis subsided. full R.O.M.
6	65	F	20	Old deformities; severe fracture of left knee	13	0.13	500 to 800	20 days		(+ to ++)•	24 hours	Arthritis unaffected, fracture much improved

0—No relief
+—Slight relief
++—Marked relief
+++—Cured

TABLE 4

RESULTS IN THE TREATMENT OF VARIOUS "NEURALGIAS" WITH INTRAVENOUS PROCAINE

Patient	Age	Sex	Duration	Description of Complaints	Number of Treatments	Dosage		Duration of Treatments	Side Reactions	Immediate Effect		Observation	Final Result
						Per Cent	Cubic Centimeters			Degree	Duration		
INTERVERTEBRAL DISKS													
1	39	F	1 month	Recurrent back pains 1 month postoperatively	4	0.1	1,000	4 days				1 month	Gradual decrease of pain: physiotherapy
2	44	F	1 week	Apprehensive, severe pain post-operatively on arising	5	0.1	500	5 days	Apprehension, tightness in chest			11 months	Gradual improvement—physiotherapy
3	42	M	3 years	3 years postoperative cordotomy and local sciatic injection no help	1	0.1	1,000	1 day		Good	?	3 weeks	No improvement: psychogenic?
4	35	F	2 years	Sciatica 2 years postoperative	1	0.1	1,000	1 day				2 weeks	No improvement: psychogenic?
5	31	F	1 month	1 month postoperative temperature, 100° F.; lumbar myositis	2	0.1	1,000	2 days		Moderate	?	1 week	Improved as temperature fell to normal
TABES DORSALIS													
1	47	M	15 years	Severe taboparesis, partial paraplegia, severe pains	9	0.13	500	6 months	Clonic tremors for half hour	0 to +	0 to 2 weeks	6 months	Progressively worse: cordotomy no help
2	60	M	10 years	Migrating lightning pains, recurring	12	0.13	500	5 months	Faintness	0 to +	0 to 1 month	5 months	No change; pains less frequent?
3	70	M	20 years	Lightning pains and paresthesias in feet	8	0.13	500	3 months		0		3 months	No change; pain not severe at treatment
4	56	F	5 years	Migrating lightning pains and hyperesthesia	15	0.13	500	6 months	Pallor and faintness	0 to ++	0 to 1 month	11 months	No change
MISCELLANEOUS													
1	65	F	15 years	Multiple sclerosis? Spasms of muscles in right leg	3	0.13	500	3 days		0 to +	4 to 6 hours	1 week	No change
2	74	F	10 years	Severe right subscapular pain every 3 to 4 weeks; arthritis	21	0.13	500 to 1,500	6 months		0		6 months	No change
3	74	M	1 month	Postherpetic neuritis; apparent mild pain	1	0.1	500	1 day		+	?	1 week	Slightly less pain

0—No relief
+—Slight relief
++—Marked relief
+++—Cured

TABLE 5

RESULTS IN THE TREATMENT OF ALLERGIC DERMATOSES WITH INTRAVENOUS PROCAINE

Patient	Age	Sex	Duration	Description of Complaints	Number of Treatments	Dosage		Duration of Treatments	Side Reactions	Immediate Effect		Final Result
						Per Cent	Cubic Centimeters			Degree	Duration	
A. SERUM REACTIONS												
1	19	F	12 hours	Severe pruritus and generalized urticaria*	1	0.13	500	45 minutes		+++	Permanent	Prompt, complete relief, no recurrence
2	21	M	3 days	Fever, joint pains, generalized swelling and urticaria	4	0.13	500 to 1,000	4 days		0 to +		Worse during 3rd treatment; required Demerol. PBZ
3	19	F	3 days	Fever, headache, joint pains, urticaria at injection site	1	0.13	500	30 minutes		++	½ hour	Recurred but milder; well 2 days later
4	18	M	1 day	Urticaria at injection site (polycystic kidneys)	1	0.2	500	30 minutes		++	Permanent	Well 2 days later
5	30	F	1 day	Fever, pruritus, headache, hives and swelling at injection site	1	0.1	500	30 minutes		+	1 hour	Well 3 days later
B. PENICILLIN REACTIONS												
1	40	M	1 week	Generalized urticaria (PBZ no help)	2	0.1	500	2 days		++	2 to 3 hours	Well after 2nd treatment
2	52	M	3 days	Generalized urticaria, fever, joint pains (PBZ no help)	2	0.13	500	2 days		+ to +++	Permanent	Well after 2nd treatment
C. MISCELLANEOUS												
1	54	M	10 months	Pruritus and generalized urticaria after 5 P.M.	1	0.13	500	45 minutes	Tremors; no complaints	+	1 hour	Gradual improvement with PBZ
2	45	F	1 year	Recurring urticaria: one previous episode for 5 months	9	0.05 to 0.1	500	6 months		0 to ++	0 to 2 months	Urticaria suddenly ceased
3	63	F	1 month	Severe generalized eczematoid dermatitis	1	0.1	500	45 minutes	Fever (101°); cause?	+		Much improved by an allergenic diet
4	42	M	2 weeks	Severe neurodermatitis disseminatus	2	0.1	500	2 days		++	8 hours to 1 day	Gradual improvement
5	72	F	1 month	Neurodermatitis disseminatus (cardiac asthma)	1	0.1	500	1 hour		+	?	?
6	74	M	1 month	Macular rash, pruritus at night—cause?	3	0.1	500	3 days		+ to ++	1 to 2 hours	No improvement

*Onset shortly after injection of serum ("immediate reaction").

TABLE 6

RESULTS OBTAINED USING ONE PER CENT SOLUTION OF PROCAINE INTRAVENOUSLY DURING LABOR IN 4 CASES*

Patient	Age	Para	Amount Given	Repair	Relief	Reactions	Recovery	Baby
1	19	0	1,500 cc.	No	+++	0	Uneventful (ether)	Good
2	21	1	300 cc.	Yes	+++	0	120 seconds	Good
3	19	0	600 cc.	Yes	+++	Twitching	90 seconds	Good
4	Records not available				+++	0	Uneventful	Good

*Given by Dr. W. E. Dotter in 1945.

these patients persisted in the treatments in the belief that the pain recurred less frequently. Our statistics failed to corroborate even this effect (see Table 4).

Graubard, et al.[14] emphasized the poor results to be expected in the treatment of pain due to direct nerve pressure. Whereas none of our patients had objective evidence of direct nerve pressure, all had symptoms suggesting some direct, painful stimulation of various sensory nerves and in all the exact etiology was unknown. This series of 82 treatments given to 12 patients illustrates the futility of using small doses of intravenous procaine for the relief of pain which is due to direct sensory nerve stimulation.

Allergic states—Thirteen patients received 29 injections of procaine intravenously for allergic dermatoses due to: sensitivity to tetanus antitoxin (5 cases), penicillin reactions (2 cases), and unknown causes (6 cases). All of these patients complained of pruritus and this was the chief indication for treatment with procaine.

It will be noted in Table 5 that all but 1 patient with serum sickness showed slight to marked immediate relief of symptoms. This was most remarkable in patient A-1, a nurse whose symptoms began within a few minutes after the injection of tetanus antitoxin. Patient A-2 was the sickest of this group and became visibly worse during his third treatment although 1,000 cc. were given. After the fourth injection he was given Pyribenzamine and was well two days later. Early administration of intravenous procaine seemed to prevent the development of fullblown serum sickness in 2 cases.

Both cases of urticaria due to penicillin showed similar good response to two injections of procaine intravenously. This response was more dramatic because Pyribenzamine had failed to be of definite help in either case.

The miscellaneous dermatoses of probable allergic, but undetermined, cause were less responsive. Immediate relief of symptoms varied, even in the same patient, from none to marked. None was cured and, although most improved, the improvement could not be attributed to the effects of intravenous procaine.

Stevenson* obtained relief in patients with pruritus ani by injection of 5 cc. of 1 per cent solution intravenously.

Presumably, then, procaine has a definite antihistaminic action and may be effective in the relief of various allergic states when Benadryl or Pyribenzamine fails.[6,7,25,27] The chief disadvantage is the inconvenience in its intravenous administration.

General anesthesia—Dotter and Stedget delivered 4 patients, using procaine intravenously as the anesthetic agent. Complete records were available on 3 of these patients and are summarized in Table 6. It will be noted that intravenous procaine was the only anesthetic agent used for patients 2 and 3, both of whom required repair of episiotomies. From 300 to 1,500 cc. of 1 per cent procaine were given intravenously for forty minutes to two hours with no ill effect except slight twitching in one case. Practically complete relief from any pain was obtained in all 4 cases; recovery from the anesthetic occurred within two minutes with no nausea, vomiting, or other after effects, and all 4 infants breathed spontaneously. Results were considered excellent in all cases. The disadvantage in obstetrics is the necessity for constant vigil while the procaine is being administered throughout the first and second stages of labor.

Cardiac arrhythmias—We have used procaine intravenously in 1 patient with myocardial infarction and ventricular tachycardia in an attempt to interrupt the erratic impulses. Three hundred fifty cubic centimeters of 0.1 per cent solution caused no untoward reaction but failed to cause any change in the cardiac rate. The patient died the following day

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of congestive failure.* We have used intravenous procaine as a supplement to cyclopropane, a well known cause of cardiac arrhythmias during the administration of anesthesia.

Uhley and Wilburne[28] produced various arrhythmias and a variety of electrocardiographic changes by rapid injection of large doses of procaine intravenously in dogs. They caution against routine use of the drug in cardiac arrhythmias because of the variable effects on the heart mechanism.

CONCLUSIONS

Procaine administered intravenously is a safe drug if it is administered under close observation. It is destroyed by hydrolysis within twenty minutes after injection and, except for the rare instances of sensitivity (none of which has been reported by any of the authors in this review), may cause only two potentially serious reactions: (1) convulsions, and (2) cardiac arrhythmias. Both may be controlled promptly by stopping or reducing the rate of injection. Addition of glucose and/or ascorbic acid reduces the incidence of convulsions.

The dosage varies with the condition being treated, the rapidity of injection, and the concentration of the solution. It may vary from 0.5 to 2 gm. in 0.1 per cent solution to 30 mg. to 15 gm. in 1 per cent solution.

Clinically, intravenous procaine may give *good* results in the following conditions:

1. Various allergic states (temporary and permanent)
   a. Serum reactions, immediate or delayed
   b. Penicillin reactions
   c. Probably other drug sensitivities
2. Pruritus of jaundice, etc. (temporary)
3. Postoperative pain, burns and trauma (temporary)
4. Vasospastic disorders (temporary and permanent)
   a. Causalgias (reflex sympathetic dystrophies)
   b. Arterial spasm (angina pectoris, gangrene, etc.)
   c. Venospasm (thrombophlebitis, etc.)
5. Bronchospasm (temporary and permanent)
6. General anesthesia where muscular relaxation is not required (as in obstetrics)

Fair results may be expected in the following conditions:

1. Osteoarthritis (temporary)
2. Chronic allergic dermatoses (temporary)
3. Acute rheumatoid arthritis (temporary or permanent)

Poor results may be expected in the following conditions:

1. Chronic rheumatoid arthritis
2. Neurologic disorders
   a. Herniated intervertebral disks
   b. Tabes dorsalis with lightning pains
   c. Neuralgias of unknown cause
   d. Various "spastic conditions" (although there may be some measure of relief during injection)

Uncertain results may be expected in the following:

1. Cardiac arrhythmias
2. Asthma (depending on the factors of allergy and bronchospasm)
3. Acute anuria

*Since this study, another case of paroxysmal ventricular tachycardia was treated with two injections of 15 cc. and 30 cc. of 1 per cent procaine with no effect and a case of paroxysmal auricular tachycardia was treated with 10 cc. of 1 per cent procaine with prompt reversion to normal sinus rhythm.

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Surgical Problems in Breast Cancer

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To any American it is a rare and distinct honor to be invited to address the Royal College of Surgeons of England and, to your distinguished President and Council of the College,† I am deeply grateful for this privilege.

CLINICAL MATERIAL

All the clinical material in our hospital is divided into the major types of clinical cancer, and around each classification a staff is built to produce men who have an unusually extensive experience and, incidentally, knowledge of a particular type of cancer, including its experimental aspects, its surgery, its irradiation therapy by radium and x-rays, and its other chemical phases which may have a place in its complete, rounded study.

Professor Burton J. Lee and I started the Breast Department in 1920, and since 1933 I have been in charge of it.

Our experience, philosophy, and conclusions are based on the care and study of 13,054 cases of breast cancer at the Memorial Hospital. Our cases of cancer of the breast are divided and classified as follows:

	Number of Cases
Primary operable	8,025
Operable after local excision elsewhere	598
Primary inoperable	1,727
Recurrent inoperable	1,824
Prophylactic	707
Sarcoma	48
Male breast cancer	125
	13,054

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†Adapted from the Moynihan Lecture delivered at *The Royal College of Surgeons of England*, 1949, and published with permission of the Annals of that organization.

Of our 13,054 cases of breast cancer, 66 per cent were considered operable. Our material today, however, is running at a higher percentage of operability—approximately 75 per cent.

INCIDENCE

We find the highest percentage of breast cancer among Hebrews. At present there is no explanation which is entirely acceptable to all. However, among the reasons given are the following:

1. As carcinoma of the cervix uteri is so very rare in Jewish women, it has been stated that they numerically make up for this lack of cervical carcinoma, by greatly increasing the amount of breast carcinoma. This gives no reason as to why the condition exists.

2. It has been stated that the reason Jewish women do not often get cervical carcinoma, is that the religious rites of circumcision are meticulously carried out and consequently that there is less opportunity for carrying infection up to the cervix, which when lacerated and infected is more apt to develop cancer.

3. The most probable reason, in my judgment, is that in the Hebrew, we are dealing with an inbred group, rarely marrying outside their own people, which could easily explain it along well recognized laws of genetics and heredity.

HIGH SELECTIVITY

There are few fields of science where there is greater discrepancy and irregularity in evaluating therapy than in the statistics of cancer. Our own philosophy is to interpret operability along very generous standards. Realizing that there is

no means of salvage to be compared with radical surgery, I am apt to give a patient the opportunity of a radical operation, which in the hands of some clinicians would be denied. I believe this to be correct. Even this broader selection, or what some might call careless selection, has given us the following results:

	PREOPERATIVE IRRADIATION RADICAL SURGERY PER CENT	IMMEDIATE SURGERY POSTOPERATIVE IRRADIATION 628 CASES IN 1942 PER CENT
The five-year salvage in the 3,988 cases (1935 to 1942)—advanced as well as operable cases	39.6	46
2,159 operable cases (treated by surgery or irradiation, or both)	54.3	60.6
1,913 operable cases (treated by radical surgery)	56.2	60.2
737 operable cases (treated by radical surgery) breast alone involved	78.6	83.8
1,173 operable cases (treated by radical surgery) breast and axilla involved	42.2	47.2

The overall cure rate, including every case—advanced as well as early—was 39.6 per cent.

In the article by Haagensen and Stout (*Ann. Surg.*, December, 1943, p. 29) 13 criteria are given which they think indicate inoperability, some singly and some criteria in combination. We fully agree that many of these criteria indicate a poor prognosis; but who has not been mistaken in his clinical estimate of a case? Who has not obtained a cure in a case when he had anticipated a failure?

One of their criteria of inoperability is ulceration. I do not agree that ulceration of the carcinoma *per se* should always indicate inoperability. It is well known that adenocarcinoma of the breast ulcerates comparatively early in its course, due to pressure necrosis against the overlying skin. We once had an adenocarcinoma of the breast which had been ulcerated for ten years. Curiously enough, at the radical operation, no node was found to be involved with cancer. We therefore have a viewpoint of ulceration quite different from these authors.

Pregnancy and lactation were also both contraindications for the radical operation in their list. Obviously, they offer a poor prognosis; but it is unthinkable, to me, that every case of pregnancy or lactation, accompanied by a breast cancer, should be thrown out of consideration for cure. Recently, in going through the records of 27 patients with pregnancy in whom cancer of the breast developed, we found 7, or 25 per cent, who had survived five years or more, following the radical surgery.

I agree as a rule on the contraindication of supraclavicular metastasis; however, there is a growing modern tendency to extend the frontiers of surgery in breast cancer. If the chest plate is negative, and the involvement of the supraclavicular area is minimal, I think it is often justified to split the clavicle or remove it and extend the operation on up into the base of the neck. A few years ago Semken presented 3 cases of breast cancer with supraclavicular involvement, who survived from six to nine years after radical mastectomy, accompanied by neck dissection.

Anyone who carefully excludes from operation every case with an apparently poor prognosis, should have a very high percentage of cure closely approaching 100 per cent by radical mastectomy of his selected material. I consider this not meeting our full responsibility as clinicians. We must insist on the report of survivals of the other material which was excluded from operation.

BIOPSY

Biopsy in breast tumors is a necessary evil. I do not minimize its possible hazards, either on theoretical or practical grounds. An excisional biopsy carelessly performed can easily be a definite hazard, and it is not a difficult matter to get so close to the tumor, as to cut accidentally into it while performing the excision. Furthermore, if the tumor be cancer, it is a fact in every case that lymphatic channels between the tumor and the axilla will be cut across; and on every theoretical ground this is wrong. Practically, however, biopsy is necessary, and cannot be avoided until some new development occurs, such as the deposit in the

tumor of an isotope which is revealed by the Geiger counter, the use of fluorescein as revealed by a violet light, similar to its use in brain tumors, or some other entirely new method of obtaining the desired information.

The following are the methods of biopsy usually employed in breast tumors: (1) excisional biopsy; (2) incisional biopsy; (3) aspiration biopsy.

To my mind, aspiration biopsy is the best method if the tumor is easily accessible—which it frequently is. Next in order, I prefer the total excision of the tumor with a good margin of surrounding tissue; and least of all, I like the incisional biopsy method of cutting directly into the tumor and removing a small portion.

Excisional Biopsy—A total excision of the tumor in question, together with a good zone of surrounding breast tissue, is one of the best types of biopsy as it gives the pathologist a satisfactory specimen for his frozen section. One should not make a single incision directly over the tumor. Many times (and this can be microscopically demonstrated), there are cancer cells in the lymphatics of the suspensory ligaments leading up from the breast to the overlying skin; it is therefore preferable to make two skin incisions, removing the skin overlying the tumor.

There is also another procedure which is helpful. Following the making of the two skin incisions, one should pull the mass containing the tumor laterally, making the dissection rather widely down to the pectoral fascia through the breast substance. One can then place two or three fingers behind the specimen, lift it upwards, and immobilize it so that the removal is facilitated, and the excision made more accurate.

Incisional Biopsy—The removal of a portion of the cancer for microscopic examination offers certain dangers of dissemination that do not exist to the same extent in the other two types of biopsy. By cutting directly into the tumor, bleeding immediately starts; during the process of removing the piece of cancer, the lymphatic spaces and blood vessels are opened, and the cancer cells are manually pushed into the open spaces during the inevitable procedure of sponging, necessary in order for the operator to see the field. The knife, hemostats, and retractors have scattered cancer cells over their surface, and the wound, including the skin immediately surrounding the wound, also has cancer cells present. This method of biopsy therefore should not be employed except when absolutely necessary as the danger, not only of immediate distant metastasis, is real but it offers a greater possibility of local recurrence than other methods.

Aspiration Biopsy—Aspiration biopsy is a form of biopsy originally developed by Martin, Ellis, and Stewart at the Memorial Hospital. The method is simple, and has the great advantage of speed in obtaining a diagnosis. It also has the important advantage of saving a patient from an additional half-hour of anesthesia and operation, a vital consideration in bad risk patients. Some physicians develop high skill in performing a biopsy by this method.

The technic is simple. The equipment necessary is a tiny needle for injection of novocain into the skin, a fine point knife to make a prick in the skin, so the needle is not gripped by the skin, a tight fitting record syringe with an 18-gauge needle, and a needle stylette to push out the cell droplet—obtained by aspirating the tumor—onto a glass slide. Another glass slide is then placed on top of the tissue droplet and a smear made of the material. The slides are then stained and read by the pathologist. The technical procedures can be done easily and the pathologist can give you a diagnosis within ten minutes. Most pathologists, without experience in this technic, will object at first; however, after a month of instruction under an expert, they get more confidence and become a great help to the clinician. This technic, therefore, has the advantages of speed in diagnosis, and of minimizing the procedure necessary to obtain a diagnosis. It also saves the re-painting, re-draping, re-gowning, and re-gloving.

Aspiration biopsy is, as a rule, performed before the patient comes to the operating room. In our hospital aspiration biopsy is practiced commonly on many types of cases, including neck nodes, lymphosarcoma nodes, breast tumors, bone tumors, chest wall tumors, lung tumors, liver tumors, and other areas, where we think the risk is not too great.

Some surgeons attain a high degree of skill in obtaining material by aspiration. One resident surgeon obtained a positive diagnosis of cancer by aspiration in 96.5 per cent of his aspirations of cancer of the breast.

Of 1,579 cases of breast carcinoma during the past five years, in which this form of biopsy was performed, 806 were done by my resident surgeons with experience in this work, having 80 failures (9.9 per cent) and obtaining a correct diagnosis of 90.1 per cent. Of the 773 cases of breast cancer in whom the aspiration biopsy was performed by doctors new to the technic there were 156 failures (20 per cent); or 80 per cent were correct.

I must state that included in these failures are cases where the tumor was situated so deep, or was so small, that the particular case was not one which should be considered fair to an estimate of this method. On the other hand, we have many times been greatly surprised to obtain a positive report when we assumed beforehand that we would not. Every case is not equally suited to this method, but it has a most useful place in breast tumors.

It should be obvious that a negative report of cancer in an aspiration biopsy indicates nothing except that the surgeon will have to take the patient to the operating room and perform a formal surgical biopsy.

The advantages of aspiration biopsy are numerous and obvious, if there is cooperation between pathologist and surgeon. It also has certain disadvantages. If the tumor is extremely hard, it is at times not easy to obtain a tissue droplet. Metastatic areas in bone are, however, constantly being diagnosed by this method. There is a possibility, if careless, of pushing the needle through the cancer into deeper tissues. We have seen the tissue droplet, when smeared and diagnosed, reveal muscle or cartilage, indicating that one had gone too deep. In one case where the aspiration biopsy was carelessly done the patient even received a pneumothorax.

EXTENSION OF SURGERY

THERE are certain areas where one might reasonably consider extension of radical surgery in breast cancer. With present-day assistance which we get from the injection of large quantities of whole blood, plasma, penicillin, proteids, phosphorus, and calcium, the frontiers of radical surgery have been pushed back and we, today, dare attempt operations which were previously denied us.

There have been many efforts during the past fifty years to develop substitutes for surgery in mammary cancer, such as x-ray and radium therapy, the cautery, electrocoagulation, and hormones, but, in my opinion, no effective substitute for meticulous radical surgery has yet been developed. In fact, the trend today is even toward more extensive surgery for cure and palliation. Considerations are before us such as the following:

(1) Extending the classic operation to include nodes at the base of the neck.

(2) Removal of the clavicle for greater exposure.

(3) The removal of the nodes along the internal mammary artery.

(4) The removal of ribs involved by breast cancer.

(5)The routine removal of the axillary vein.

(6) An interscapulothoracic amputation, sweeping off neck and axillary nodes.

I feel strongly that the substitution of the radical mastectomy by simple mastectomy and the addition of irradiation therapy, is costly in lives and wrong in principle because irradiation therapy will not cure mammary cancer with any degree of consistency, particularly in the axilla where it may cause necrosis of one involved node and leave completely viable a similar node which received the identical amount of irradiation.

A study of the lymphatic system reveals that most of the breast drains its lymphatic contents into the base of the axilla; however, it is known that the upper inner quadrant of the breast drains not only into the axillary nodes, but there are some lymphatic channels which drain directly anterior to the clavicle and into the supraclavicular nodes. Therefore in that case, having its cancer so situated, if its supraclavicular nodes were involved with disease, it could conceivably be successfully reached and cured.

Cancer as a rule metastasizes first into the base of the axilla (Group I nodes); it then extends along the subclavian vein to the axis group behind the pectoralis minor (Group II nodes); it extends from there into three possible directions: (a) medially to nodes at the falciform ligament (Group III nodes); (b) extension upward into the base of the neck; and (c) into the sulcus along the high mediastinum.

We already know that it is occasionally possible to effect a cure if a low neck dissection is done. This is a matter of record. On the other hand, one must judiciously consider the advisability of such an extensive procedure, as one must balance the total sum of additional lives salvaged, against those lost by this combined surgical procedure. It is the rare case which lends itself to an extension of the radical mastectomy on up to include the low neck nodes. However, this setting at times does exist in the absence of lung metastasis. And it is in this case that the middle half of the clavicle or the entire clavicle may be removed and a block dissection of the low neck nodes made, sweeping the tissue downward in continuity, together with all tissues of the axillary and breast specimens. The deformity of the shoulder and arm is less than anticipated, and the function is good.

It has been suggested by Neuhof (Neuhof, H.: Excision of axillary vein in the radical operation for carcinoma of the breast. *Ann. Surg.* 108:15-20, 1938) several years ago, that the axillary vein be routinely removed at radical mastectomy. More recently MacDonald (MacDonald, Ian: Resection of the axillary vein in radical mastectomy. *Cancer,* Vol. 1, No. 4, p. 618) has advocated the routine *en bloc* removal

of the axillary vein and its surrounding fat and lymphatic tissue. This procedure of Neuhof and of MacDonald, although adding to the more complete cleaning out of the axilla, certainly as a routine procedure, brings up for consideration the investigation of the competency of the cephalic vein in every case before one dares carry it out.

Occasionally in a case where the lungs are negative, and when there is involvement of the nodes of the low neck, an interscapulothoracic amputation is thoroughly justified. We think this operation especially useful in those cases where radiation damage to supraclavicular skin is painful in the presence of disease. By this procedure the nodes of the lower neck, together with all lymphoid and fat issue, the clavicle, scapula and arm, will be swept off cleanly from the first and second rib area. This is admittedly a drastic procedure, but there are certain urgent instances where, for special reasons, this procedure is more than justified; and where the life of an otherwise doomed patient may be salvaged.

MILK FACTOR

The easiest explanation of the hereditary factor, if it could be proved, would be the existence of a milk factor in the human, similar to that proved in the mouse. However, my own efforts at proving the existence of a milk factor in the human have not proved its existence. The difficulty of establishing the milk factor is that in so comparatively few cases is it possible to get critical information as to whether the mother nursed the child, whether the grandmother nursed her child, etc. Human lives last so long today that it is difficult to establish in a given case of a woman who developed breast cancer, that she, as a baby, was breast fed. Such a study, to be valuable, would of necessity have to cover a long number of years. Fifty per cent of my cases studied had been breast fed and 50 per cent had not, leaving us with no evidence.

On the other hand, the existence of a milk factor in mice has been so firmly established by both Little and by Bittner, that we must accept the idea. And it gives us all a thrill to realize that with the discovery of the milk factor, a virus-like body in the milk of inbred strains of laboratory mice, that Bittner has been able to develop an antibody against the development of breast cancer in the mouse. This comparatively recent discovery has shed a new ray of hope on the possible future control of breast cancer, if it were possible to transfer the idea to the human. Although this virus-like body can be established in mice, efforts to prove its existence in either rats or the human have as yet failed.

HEREDITY

Anyone who has had the opportunity to study large numbers of human cases of breast cancer will sooner or later be impressed with the presence of an hereditary factor. It will not hold good in all cases, but the occasional case exhibits the hereditary aspect most strikingly. A few years ago, in my hospital ward, there were two instances of mother and daughter, all with breast cancer. All were there at the same time. We have had in our care a mother and 4 daughters, all of whom developed breast cancer at about the same age—46 years. The hereditary influence in breast cancer is so common that it no longer impresses us. It is our observation that this influence is through the maternal side of the family rather than through the paternal side. We have also been interested with its presence in identical twins.

END RESULTS

Due to great improvements in our records, a consideration of material for this paper will not be made prior to 1932. Our study of 7,394 cases will be limited to mammary cancer in women only, between January 1, 1932, and December 31, 1947. However, as we cannot report five-year follow-up on cases later than December 31, 1942, it further reduces the cases to 3,988.

Table 1 gives the complete analysis of the 3,988 cases analyzed by years. It is obvious that those cases treated (1935 to and including 1939) by preoperative irradiation followed by the radical mastectomy were not as successfully treated as the 1940, 1941, and 1942 cases where immediate radical was followed by postoperative x-ray therapy in those cases having axillary involvement.

When Table 1 is analyzed it is noted that the 329 primary operable cases of 1942 treated by the radical mastectomy yielded the following five-year survivals:

Breast alone involved	83.8 per cent
Breast and axilla involved	47.2 per cent

This brings one to a point which in my view is

TABLE 1

FIVE-YEAR SURVIVAL RATES AMONG PATIENTS WITH BREAST CANCER ADMITTED FROM 1935 THROUGH 1942, INCLUDES ALL CANCER CASES, ADVANCED AS WELL AS EARLY CASES

		SURGERY			PREOPERATIVE IRRADIATION AND SURGERY				
		1942	1941	1940	1939	1938	1937	1936	1935
TOTAL NUMBER OF PATIENTS	3,988	628	618	611	458	455	428	436	354
Indeterminate Group:									
Applied after treatment elsewhere—no evidence of cancer	152	31	14	25	23	19	14	14	12
Consultation only—no treatment	28	3	2	2	3	2	7	6	3
Patient refused treatment or palliation	235	35	49	26	20	32	23	26	24
Dead within five years of other causes without recurrence	131	24	23	24	17	8	11	13	11
Lost track of within five years without recurrence	87	29	16	13	4	11	8	2	4
Total indeterminate results	633	122	104	90	67	72	63	61	54
Determinate Group (Total number minus indeterminate group)	3,355	506	514	521	391	383	365	375	300
Percentage surviving five years	39.6	46	438	44	386	366	37.3	30.1	34.0
Primary operable cases (Determinate); some were treated by irradiation only	2,159	348	360	349	255	245	218	221	163
Percentage surviving five years	54.3	60.6	55	57.3	52.9	53.4	55	43	50.3
Primary operable cases treated by radical mastectomy (Determinate)	1,913	329	337	329	222	211	180	179	126
Percentage surviving five years	56.2	60.2	55.2	58.4	54.5	56.9	58.3	47.5	54.8
Primary operable cases treated by radical mastectomy (Determinate); breast alone involved	737	117	126	127	89	73	85	73	47
Percentage surviving five years	78.6	83.8	82.5	80.3	68.5	89	75.3	63	82.9
Primary operable cases treated by radical mastectomy (Determinate); both breast and axilla involved	1,173	212	211	202	132	138	93	106	79
Percentage surviving five years	42.2	47.2	38.9	44.6	45.5	39.9	41.9	36	37.9

timely for consideration. In the reporting of end results of therapy, each investigator has different criteria for the handling of his material; some report five-year survivals; some report five-year cures, meaning those cases are free of recurrence as far as the doctor can ascertain; some report ten- and fifteen-year survivals. A congress of competent medical statisticians from all over the world should meet, study the different viewpoints, and arrive at an acceptable conclusion as to the proper way to handle cancer material statistically. In my own case, all the figures are arrived at by the statistical department, a new branch in the hospital. We, as surgeons, ask that certain statistical problems be developed, but have no personal part in their development.

There is a great difference in the life history of different types of cancer as to recurrence. For instance, cancer of the lip, skin, cervix uteri, stomach, lung, etc., have in common the fact that if there is no demonstrable disease at the end of five years, cure is usually assured in these cases. Their survival curve at the end of the five years does not continue to drop, but straightens out. On the other hand, melanoma of the eye is peculiar unto itself. Following enucleation of the eye for melanoma metastasis often takes place in the liver twenty-five to thirty years later.

Likewise, cancer of the breast has a recurrence and metastasis rate peculiar to itself. At the end of five years of freedom from recurrence or metastasis, there is still a 10 to 11 per cent cancer fatality in those cases which were free from disease at the end of five years. On further analysis of this problem, one is astonished to realize that in those operable cases with axillary lymph node involvement, the rate of subsequent death from cancer goes up to 24.1 per cent in those cases operated on sixteen years previously. (See Table 2.)

In order to compare some earlier groups of cases we took the operable cases of 1932 and 1933 who had radical mastectomies. We found

TABLE 2

PERCENTAGE OF PATIENTS FREE OF DISEASE AT FIVE YEARS WHO LATER DIED OF CANCER—ANALYZED BY STAGE OF DISEASE—PRIMARY OPERABLE CASES TREATED BY RADICAL

	ADMITTED 1940-1942		ADMITTED 1935-1939		ADMITTED 1932-1933	
TOTAL CASES FREE OF DISEASE AT FIVE YEARS	Breast only Involved 287	Breast and Axilla 228	Breast only Involved 260	Breast and Axilla 178	Breast only Involved 40	Breast and Axilla 29
Percentage of cases free of disease at five years who later died of cancer		5.3	9.2	14.0	10.0	24.1

that the greater the number of years after the radical, the higher the sum percentage of recurrences. Table 2 reveals that those having axillary involvement are much more apt to have a late metastasis or recurrence than those having their disease confined to the breast at the time of operation.

It would appear that those operable cases having disease confined to the breast receiving an immediate radical, fared better than those who were given preoperative irradiation. (Table 3.)

SIZE OF THE CANCER

THE ultimate results of therapy are based on several variable factors, namely, degree of malignancy, the age of the patient, the richness of the soil, the size of the tumor. In a study of the effect of tumor size on the result of treatment by radical mastectomy during the years 1935 to 1942, we found that the smaller the tumor, the greater the percentage of five-year survivals. In a small series of 22 cases with a diameter of 1 cm. or less, the survival rate was 93 per cent. (See Table 4.)

AXILLARY NODE INVOLVEMENT

In a study of node level involvement in primary operable cases treated by radical mastectomy we find the following:

	LEVEL I	LEVEL II	LEVEL III
Five-year survivals	65.2 per cent	44.9 per cent	28.4 per cent

Our survival rate for those 279 determinate cases having disease confined to the breast is 83.2 per cent. Four hundred and fifty-one cases with axillary involvement were tagged with an aluminum tag at the base, the midportion, and the apex of the axilla representing levels I, II, and III. The five-year survivals in this group were 44.3 per cent.

LYMPHEDEMA

Next to effecting a cure in breast cancer, the greatest surgical problem involved in this field is lymphedema of the arm. Owing to the importance of avoiding the condition, it might be profitable to consider briefly the causes of lymphedema. They are the following:

1. Massive bacterial infection of the axilla.
2. Primary and metastatic disease in the axilla.
3. Obesity.
4. Heavy x-ray therapy of the axilla.
5. Lack of thorough postoperative drainage of the axilla, resulting in lymphangitis.
6. Filariasis.
7. Surgical operation with perfect wound healing; exact cause of lymphedema unknown.

Discussions here will be limited to lymphedema in relation to breast cancer. Lymphedema which is due to metastatic disease is permanent and irreparable.

In our opinion all patients who have had a proper radical mastectomy have an arm which is slightly larger than the opposite arm. During the course of the radical removal of all lymphatic chains, small veins, and axillary fat, it is to be anticipated that there will be a minimal impairment of the return lymphatic and venous circulation. This is due not only to the removal of many channels of egress from the arm, but also because there will be laid down as a part of the repair process, extra scar tissue which helps to obstruct fluid return and which lessens the caliber of vein and lymphatic channels of the local region.

I wish to emphasize that the postoperative care of the wound of a patient who has had a radical mastectomy is of importance equal to

TABLE 3

DETERMINATE RESULTS	ADMITTED 1940-1942	ADMITTED 1935-1939	ADMITTED 1932-1933
Primary operable cases treated with radical; breast alone involved	370	367	58
Percentage surviving five years	82.2	74.9	75.9
Primary operable cases treated with radical; breast and axilla involved	625	548	124
Percentage surviving five years	43.5	40.7	31.5
Primary operable cases treated with radical; breast alone involved			
Percentage free of disease at five years	77.6	70.8	69.0
Primary operable cases treated with radical; breast and axilla involved			
Percentage free of disease at five years	36.5	32.5	23.4

the care with which the axillary dissection is carried out. The surgeon in charge should not leave the responsibility of the surgical dressings entirely to the young assistant. As the responsibility is too great, someone of experience, who is keen in detecting small fluid accumulations, should not only carefully investigate the wound, but should inspect the wound within the proper postoperative period, namely, the third or fourth day, or *before* the time that the glazed appearance of the granulation tissue forms, which accompanies fluid collection.

If effective axillary drainage is instituted early, following the radical, there will be little opportunity for massive lymphedema of the arm, unless the case was on the borderline of operability. However, if neglect of a sizeable axillary accumulation continues for a period of four or five days, the chances are that permanent lymphedema will be produced. The greatest preventive measure of lymphedema is meticulous care of the postoperative wound.

The immediate effect of heavy x-ray therapy to the axilla is an inflammatory reaction of the skin of the axilla, upper arm, and supraclavicular areas, which will impair superficial lymphatic return. The late effects of such irradiation therapy is the laying down of an additional amount of fibrous tissue which further produces lymphedema. There is an amount of x-ray therapy over the axilla past which we should not go. Unfortunately, we dare not use a cancericidal dose of x-ray in the axilla without, in most instances, producing a lymphedema.

THE life of a patient with a lymphedematous arm is miserable; her future is progressively worse. Not only is the weight of the arm heavy, but it feels to the patient as if it would burst. Discomfort is continuous. Localized infection and cellulitis are common. Unfortunately, there is little relief available for these sufferers. Any measure which can be employed to prevent this

TABLE 4

FIVE-YEAR SURVIVAL ACCORDING TO TUMOR SIZE

LARGEST DIAMETER OF PRIMARY TUMOR	TOTAL CASES	BREAST ONLY INVOLVED	BREAST AND AXILLA INVOLVED
Less than 2 cm.	201	121	80
Percentage surviving five years	78.1	90.0	58.8
2.0 to 2.9 cm.	397	185	211
Percentage surviving five years	67.3	78.9	56.9
3.0 to 3.9 cm.	316	117	199
Percentage surviving five years	54.7	72.6	44.2
4.0 to 4.9 cm.	183	65	118
Percentage surviving five years	51.9	67.6	43.2

condition should be faithfully resorted to. In my hands the Handley lymphangioplasty has been a disappointing procedure, as has also the Kondoleon operation. As lymphedema increases, so does the incidence of arm infection. The Kondoleon operation has contributed but little to the improvement in the size of the arm; but in large arms accompanied by frequent infections, the procedure has proved to be of real value in reducing the number of acute attacks of cellulitis and arm infection; in some instances the infections have been stopped altogether.

The procedures of Reinhoff, and of Hutchins, in the transplantation of the latissimus dorsi muscle have, like other procedures for the relief of this condition, proved disappointing. The Treves procedure of detaching the teres major muscle from the humerus and attaching it to the under surface of the remaining portion of pectoralis major muscle is still to be evaluated.

As cancer of the breast is the most common type of cancer attacking women, there are, therefore, an enormous number of cases of lymphedema. There is no field of breast surgery more worthy of research than the alleviation of or relief from lymphedema.

SKIN GRAFT

The controversy as to the necessity of a skin graft in every radical mastectomy is still going on in the United States. I feel that in the majority of cases a skin graft is not necessary. Nowadays patients come with smaller tumors than previously, giving us the opportunity to make the incision a good distance from the tumor and still get a primary closure. However, in certain instances, particularly in the upper inner quadrant, skin graft often becomes necessary.

On the other hand, some surgeons skin graft every radical. This viewpoint we oppose as unnecessary. Furthermore, those advocates have to date been unable to prove that by skin graft they obtain a lesser number of skin recurrences than those who do not carry it out as a routine.

White has recently studied local recurrences in three hospitals, comparing those who had a plastic closure with those who had a skin graft. The results were as follows:

Local Recurrence	*Five-year Results Disease limited to breast*	
Roosevelt Hospital	Plastic	10.8 per cent
Presbyterian Hospital	Graft	9.7 per cent
Henry Ford Hospital	Plastic	5.5 per cent
	Graft	8.3 per cent

We believe that the best method of avoiding a local recurrence is to leave a generous margin on all sides of the tumor, cut very thin flaps according to Handley's principles, and make a skin graft only if necessary.

The use of the opposite breast for purposes of facilitating closure has never been developed to the point that it should be used. Its use will frequently aid in making a closure that would otherwise require a graft.

POSTOPERATIVE DEATHS

By postoperative death, we mean that the patient on whom we have performed radical mastectomy does not leave the hospital alive. The number of postoperative deaths from the radical mastectomy has greatly improved during the last ten years. The report of Lewis and Reinhoff from Johns Hopkins Hospital, the home of the radical mastectomy, was 5 per cent, i.e., one death in 20 cases. The Henry Ford Hospital reported 4 per cent, i.e., one in 25 cases. The Presbyterian Hospital reported 3 per cent, i.e., one death in each 33 cases.

Between the years 1935 and 1940, during the preoperative irradiation years, we had several deaths from infection. The postoperative wounds of those who received preoperative irradiation followed by the radical, were very poor. The healing qualities of the normal skin flaps were greatly impaired by radiation. As we increased the amount of radiation, the quality of healing deteriorated. Following this five-year experience, we did the immediate radical mastectomy and followed the cases with postoperative irradiation over the axilla, supraclavicular and infraclavicular areas, if the axillae were involved. From the start of this regimen to the present, our operative mortality has decreased to 0.3 per cent, or one death in each 325 cases. These deaths have been chiefly cerebral accidents in women with blood pressures of over 230, or cases of coronary thrombosis, or pulmonary embolus.

During the nine-year period of 1939 to 1948, 4,544 radical mastectomies were performed. The 14 operative deaths were due to the following causes:

Pulmonary embolus	5 cases
Cerebral accident	4 cases
Coronary or cardiac	3 cases
Shock	1 case
Uncontrolled diabetes	1 case
Infection	0

The above list shows that infections which were the chief cause of postoperative death during the preceding five years completely disappeared from our causes of death.

PAPILLOMATOSIS

Sanguinous or serosanguinous discharge from the nipple is indicative of the presence of a papilloma, or papillary cyst adenoma or carcinoma. It has been the teaching of the past that a papilloma should be removed because it frequently develops into carcinoma. It is the practice of surgeons to remove the papilloma locally or perform a simple mastectomy, if they could not palpate the lesion. If the lesion appears to have the characteristics of a precancerous papilloma surgeons usually do a simple mastectomy.

About eight years ago we raised the question as to how the pathologist could unequivocally predict that what he thought to be a precancerous papilloma would actually continue along the line indicated by the ominous appearance and actually develop into cancer. We thought it would be worth while to test out the established viewpoint. Consequently, we ceased performing a simple mastectomy on even those cases with the direst reports of the precancerous state, and even those cases with reports warning us that this was a lesion which appeared particularly apt to develop into cancer. We fully recognized our responsibility and at first were often worried over our position. However, we are happy to report that as far as we know, not one case of papillomatosis has developed a cancer to date. During these eight years there have been approximately 416 cases of papillomatosis, many of which had developed marked precancerous appearance. The fact that none of these cases had developed cancer makes one recognize that (a) papillomatosis is not a precancerous lesion; (b) that the appearance of precancerous attributes in the papilloma is a false appearance, and (c) that the generally accepted and well established viewpoint concerning the development of papilloma into cancer is false. These are bold statements, but I am sure that as a rule they are true.

We then come to the next viewpoint, that the papilloma is a benign lesion and remains benign; and those cases of bleeding nipple with cancer as the cause of the bleeding, began as carcinoma—and did not develop from a previously benign papilloma. There are pathologists who state that they can trace the steps resulting in carcinoma from a papilloma, but we must disagree with their deductions and conclusions from their evidence.

In my experience the majority of papillomas are situated close to the nipple, within or at the edge of the areola, while the carcinomata which produce bloody discharge are apt to be located further out in the mid zone.

From this viewpoint it is obvious that much mutilating surgery will be unnecessary.

CYSTS

There is an enormous amount of confusion as to what procedure is best in cases of cysts, cystic disease, and cystic mastitis. These three terms for practical purposes may be used synonymously. World literature on the subject is conflicting, leaving the reader in a quandary as to whether cystic disease is precancerous, and if so what should be the surgical procedure indicated. One school of thought says that cystic disease represents a precancerous state. Among other proofs of evidence Shields Warren of Harvard proves his contention that these conditions are precancerous by statistical studies of cystic mastitis when compared with the general population of Toronto and Boston.

Our personal viewpoint is quite the contrary. We do not believe that cysts, cystic mastitis, and cystic disease are precancerous lesions. In fact, if cancer subsequently develops in a breast following the removal of a cyst or area of cystic mastitis, it does not occur in the cyst wall, but it develops in the interstitial tissue, between the multiple cysts.

We feel that this condition represents a hormone deficiency disease, probably ovarian in origin. It not infrequently occurs that breast cysts develop within a month or two following the removal of the ovaries.

The average age at which cysts most frequently develop is 44 years. The average age of menopause in New York is 46½ years. The life history of cystic disease is represented first by microscopic cysts, and dilatations along the ducts. This picture is seen usually from about 35 to 40 years of age. From then on we may find cysts of varying sizes which may have become large enough to come into the field of clinical observation. At this time one may literally find hundreds of tiny miniature blue cysts, 1 or 2 mm. in diameter. As ovarian function decreases, cystic disease increases.

It is my belief that cysts and cystic disease are so common in females that the condition is not far from normal for one who is approaching her menopause. In those women who develop multiple cysts, they as a rule continue to develop cysts up to and until the actual menopause. With the complete cessation of menstrual periods, the cysts spontaneously disappear, and do not return. It is most unusual for a single cyst to develop in the twenties or early thirties, or past 60 years of age. If one does, there is something unusual in the output of the ovarian hormones.

As this disease is self limiting, has a normal period of development, and spontaneously disappears with the menopause, the attitude of the surgeon toward the problem should be along the line of understanding its life history. It is obvious that if a cyst appears, his first obligation to the patient is to make the diagnosis definite. This he may do in two ways. If the cyst is large, it is usually an easy matter to aspirate the cyst. If the fluid is clear, amber, or cloudy, one is dealing with a simple cyst. If the cyst be deep in the breast, is only approximately 1 to 1.5 cm. in diameter, it often becomes necessary to remove the lesion locally to establish the diagnosis definitely. At this size, the lesion is hard and fluctuation cannot be elicited. We strongly oppose the idea of a simple mastectomy for cystic disease. In my opinion there is no place where more unnecessary surgery is done than in cystic disease.

Having established the diagnosis, and remembering that it is usually a bilateral disease, our habit is then to check the condition of the breast periodically, at six-month intervals, until the arrival of the menopause. We do not keep on operating on every new cyst that develops. Following the establishment of the diagnosis, more cysts as a rule develop from time to time. If the patient is in the age between 37 and her menopause; if she has a rounded tumor which is slightly tender to palpation; and if the tumor is free from any of the classic signs of cancer, we keep checking that case, rather than repeat the operation. In an experience of approximately 400 cyst cases, I have only had to operate for subsequent breast cancer three times. Keeping this group of cases under observation two or three times a year, we are able to check on their condition and pick up any carcinoma in an early stage if one develops.

Improvement in Results

During the past fifteen years there have been definite improvements in results of therapy of operable cases of breast cancer who received radical mastectomy. This is brought out by the following:

Five-Year Survivals in Cases Treated by Radical Mastectomy

	1940-1942	1932-1933
Breast alone involved ...	82.2 per cent	77.6 per cent
Breast and axilla involved.	43.5 per cent	31.5 per cent

As would be anticipated there is not much improvement in those operable cases treated by radical mastectomy when the disease is confined to the breast—only 6 per cent. On the other hand there is great encouragement for us in those cases where the disease involves both breast and axilla; here the improvement reaches the astonishing figure of 38 per cent.

There are two ways to explain this improvement. In the first place we believe that volume of surgical experience counts for something. For the past few years over 600 radical mastectomies are performed each year on my service; and I personally do 250 a year. When my own results are compared with those of my house officers and assistants, we find in those cases having axillary involvement that my percentage of five-year survivals is 4 per cent better than theirs. This signifies that one more case in every 25 of those with axillary involvement operated on by one with greater experience, will survive the five-year period than those done by the younger, less experienced house officers who are learning how to perform the operation.

Careful handling of cancer material during the course of the axillary dissection is of greatest importance. It is even probable that some cases with voluminous axillary involvement are made worse by the operation. We find it human and almost universal that a young surgeon has a strong urge to touch the node involved with cancer, either with hand or instrument. As the axillary areolar tissue is being brought down from above the level of the axillary and subclavian veins, and from over the brachial plexus, it should be covered with gauze pads to keep the operator's glove from touching diseased tissue, thereby minimizing any dissemination. This may all seem too trivial to speak of, but such points obviously are what should be emphasized and never are.

The second, and probably the most important

cause for improvement in results of therapy, is the fact that our patients come earlier to surgeons than formerly. This is not to be proved by the percentage of operable cases coming with involved axillae. In fact we are disappointed to realize that our operable material still comes with 60 to 62 per cent having axillary involvement. However, the important improvement shows itself in the volume of disease found in the axilla at operation. Less and less cases come with bulky axillary disease.

In closing we wish to state that advocates of radical surgery have waited long and impatiently for improvements to take place. However, there are signs on every hand of improvement.

In mammary cancer, the sparks fly wide, and it is still one of our most dreaded types of cancer. On the other hand, it is one of our most curable. We believe that constant improvement in the results of therapy are taking place and can further take place in the operable cases, due to greater skill in surgery and to the earlier appearance of the patients.

Probably one of our greatest reasons for encouragement in breast cancer is just being developed in the hormone field. We now know that certain chemicals have the power to heal the ulcers of breast cancer, to fill in areas of destroyed bone, to relieve pain and disability, to overcome the anemia of cachexia by doubling the amount of hemoglobin; and the hormone can even give a sense of well being. Any chemical agent which can perform such a miracle should be speedily and urgently investigated by teams of chemists, biologists, and clinicians. There are now 600 chemicals whose values remain to be studied. The next ten years of hormone investigation may well prove to be the most important decade since the introduction of the radical mastectomy.

OPHTHALMOSCOPE DEVELOPED 100 YEARS AGO

PROMINENT AMONG THE NAMES of investigators whose work has advanced the practice of medicine is that of Herman von Helmholtz (1821-94), discoverer of the ophthalmoscope. In recognition of the 100th anniversary of this outstanding achievement, Edmund Kopietz, *Postgraduate Medicine* cover artist, has featured Helmholtz this month.

Helmholtz was first recognized for his paper "On the Conservation of Energy," which led to his appointment as Professor of Physiology at Königsberg University. In his research there, he established, by electrical means, the rate of transmission of nerve impulses. Following his monumental development of the ophthalmoscope, he continued his researches on color and the mechanism of accommodation, work which confirmed and elaborated conclusions reached by Thomas Young, a pioneer British ophthalmologist. Oddly enough, Helmholtz first regarded the ophthalmoscope as of little scientific and practical value; the instrument's great worth in medical diagnosis has, of course, long since been proved.

In addition to his fundamental research on the physiology of the eye, Helmholtz also made many advances in the field of acoustics and showed the relation of mathematics to music in a classic discussion on "Sensations of Tone."

Appointed Professor of Physics in Berlin in 1871, Helmholtz remained there until 1885 when he became president of the government's Physico-Technical Institute, where he continued his scientific endeavors in physiology and physics.

Reprints of the cover painting, suitable for framing, are available from *Postgraduate Medicine,* 516 Essex Building, Minneapolis 3, Minnesota. Price $1.00.

Diagnostic Clinic

Differential Diagnosis of Enlargements of the Kidney

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THE urologist is more and more encroaching upon the fields of, or crossing swords with, those who are engaged in general abdominal diagnosis. It is because of this fact that his problems are more widespread than they formerly were. It occurred to me that it might be interesting to discuss the differential diagnosis of things that make the kidney increase in size and that may be confused with an enlarged kidney.

The lesions that cause enlargement of the kidney can be very easily divided into two groups: (1) common lesions one sees in everyday practice and (2) rare lesions.

What are some of the common lesions? Perhaps hydronephrosis should head the list because it is very common and very variable in degree; it often has no symptoms at all, sometimes has symptoms that can be recognized as being hydronephrotic in origin. Many times the problem cannot be solved without resort to special methods of investigation.

Next in order of frequency is probably tumor. Tumors of the kidney are divisible into two groups: (1) benign and (2) malignant. I have seen only one or two benign cases in my life. Therefore, when a patient presents himself with what you suspect may possibly be a renal tumor, the chances are 99.9 out of 100 that the tumor is malignant and the time for action is right at hand; there should be no procrastination.

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Presented before the 34th Annual Assembly of the Interstate Postgraduate Medical Association of North America, Philadelphia, Pennsylvania.

I should also like to stress one fact in the examination of renal tumors: that the patients not be palpated too frequently, too roughly nor too long. On my service at the Presbyterian Hospital, particularly in children with Wilms' tumor, once the diagnosis is made there is no further palpation. I believe that rough palpation is responsible in some cases for metastases.

Tuberculosis, although very much on the decrease—and cases of renal tuberculosis are becoming more and more infrequent, due, of course, to the marvelous results obtained in the campaign against tuberculosis—sometimes is unrecognized in a patient and goes on for a very long time. One still sees large tuberculous kidneys with enormous amounts of perirenal sclerosis.

The stone kidney occasionally is a big kidney, particularly in the case of large branched stones where the stone produces obstruction with some dilatation, plus a superimposed infection, and especially where the patient has chills, fever and sweats.

Unfortunately today with the antibiotics, with penicillin, the sulfonamide drugs and agents of that sort, we fail to realize that the No. 1 treatment for any patient is the establishment of the diagnosis, and it is also unfortunate that instead of making a diagnosis we reach for penicillin or streptomycin. All too frequently in a large clinic one sees patients who have large stones with enlargement of the kidney who have been treated for months on end with these drugs, to no avail. Had a simple roentgenogram been taken instead of a routine urinary analysis, it

would have been obvious that the treatment for the enlarged kidney was the knife and not antibiotics.

The so-called solitary cyst produces enlargements of the kidney. Such cysts are generally smooth, round and attached to the kidney; they move with the kidney, are not painful, and often are asymptomatic, so that they may be discovered on routine physical examination. It is very difficult to make a differential diagnosis by palpation alone between a malignant tumor and a solitary cyst. It is to be remembered that these solitary cysts are not solitary—solitary is the old word for them. A great many times they are multiple cysts. These cysts were formerly classified as urinary or hemorrhagic cysts, depending on their contents.

In the management of the enlarged kidney due to this cause, treatment should consist in removing the cyst and not removing the kidney. In a certain number of instances the disease becomes bilateral. What are you going to do with a patient after one kidney is out and cysts continue to grow in the other kidney? You can't very well take out that kidney. That happens every once in a while.

In contrast with polycystic disease of the kidney, there may be an enlargement of the kidney which is generally bilateral. I wish to disagree with those who state that polycystic disease of the kidney is a unilateral disease. In my experience it is always bilateral. The diagnosis when the patient comes in is generally very simple. The patient has a long-standing history of urinary troubles. Physical examination shows the presence of bilateral enlargements in the renal area. They may or may not be smooth. There is an increase in the blood pressure; there is some albumin in the urine. With that sort of clinical picture the diagnosis is perfectly obvious and establishes itself at once.

Then, of course, you make your x-rays and your blood chemistry, which nearly always shows an increase. But the most important part in the diagnosis of this type of kidney lesion is the history. I have never yet seen a patient with a bilateral polycystic disease of the kidney in whom I could not obtain a family history either of polycystic disease of the kidney or something that obviously is the result of a polycystic kidney. The patient may say that his father or mother, uncle or cousin or brother or sister or somebody died of Bright's disease. The patient may say that the person about whom you inquired had high blood pressure and died of kidney disease with high blood pressure. In other words, it is very easy, if one takes the time, to piece together out of the family history something that signifies or would at least point to the possibility of polycystic kidney disease.

HERMAN L. KRETSCHMER

In some patients who have an enlargement on one or the other side, that enlargement is due to compensatory hypertrophy of the kidney. The compensatory hypertrophy may be acquired, as the enlargement of one kidney when its mate has been removed for some disease process. On the other hand, the compensatory hypertrophy may be congenital; the patient may have been born with only one solitary, single kidney; or the patient may have an atrophic pyelonephritis on the opposite side, or a congenital failure—an aplasia of the kidney—so that its mate undergoes hypertrophy and makes an enlargement.

If one bears this possibility in mind one will not be misled into diagnosing tumors and other things that are not very obvious, perhaps, at the time the examination is made.

THERE are some rare causes that I think are well to bear in mind because they are rare and because they do occur. The rare causes may

be congenital. A patient may be born with but one renal mass. A patient's renal tissue may be fused into one kidney on one side so that he has a normal amount of secreting renal tissue but that amount has been fused on either the left or right side, either high or low. Particularly if it is low it may be confused with other abdominal lesions; when it is in the renal area it is not so confusing.

A patient sometimes comes in with a horseshoe kidney which is perfectly evident from the plane x-ray findings and on physical examination. It presents as a tumor in the midline. It extends to one side and to the other side of the midline, and if one thinks about it, it is not difficult to make a tentative diagnosis, and I am trying to emphasize *tentative diagnoses.*

Some of the uncommon enlargements of the kidney are due to leukemia. Patients may come in with an enlarged kidney that has been bleeding, and may have been told that the kidney is enlarged and there is a kidney tumor. A simple blood count, of course, disproves that at once. The leukemic enlargement may be of the lymphatic or the splenomedullary type. It is well to remember that splenomedullary leukemia, besides causing enlargement of the kidney, causes enlargement of the spleen, as I shall mention later.

In an occasional case the urologist sees a patient with leukemia who has sexual symptoms. The patient may have a priapism due to leukemic infiltration in the corpus spongiosum. I think if we bear that possibility in mind we save the patient a great deal of unnecessary examination and a great deal of time. I saw a patient not long ago who had been treated for priapism for three months. It followed him all the way through the United States from Los Angeles to Indiana. Simply listening to the story and making a palpation of the abdomen which showed an enlarged spleen was sufficient to make a diagnosis of priapism due to leukemia. Here was a simple, open and shut diagnostic problem that could have been solved if the man had had a correct diagnosis six months before I saw him.

Hodgkin's disease occasionally produces enlargement of the retroperitoneal lymph glands. Hodgkin's infiltration of the kidney produces enlargement of the kidney.

Echinococcus disease produces enlargement of the kidney, often confused with tumor. If it is remembered that the echinococcus cyst has a tendency to have lime deposited in it (and these deposits of lime are quite characteristic), and if a complement fixation test is made, one would have very little trouble in arriving at the correct diagnosis.

Carbuncle of the kidney produces an enormous enlargement of the kidney. The diagnosis can be made over the long distance telephone. The patient generally has had an infection some place, a boil or a carbuncle, pleurisy, an abscess in the skin or a lesion between the toes, a long course of fever, six, eight and ten weeks, with the presence of a swelling, and the diagnosis, of course, is perfectly obvious.

Actinomycosis, while rare, does produce enlargements of the kidney. The pyelogram may be confused with that of tumor. The picture is not that of tumor. A careful search of the urine for actinomyces establishes the diagnosis without any trouble.

Thrombosis of the renal vein may make an enlarged kidney, but is very uncommon.

Last, but not least, amyloid degeneration of a kidney causes enlargement of the kidney. It may be secondary, as it frequently is, to tuberculosis of the opposite kidney, and if the opposite kidney is small, secretes urine, is loaded with pus, and if there are tubercle bacilli present, one is apt to misinterpret the findings. The enlargement is not due to the tuberculosis; it is due to amyloid degeneration and the tuberculosis is on the other side.

After one establishes as well as he can something about the renal problem, what other things are confused with enlargement of the kidney? Enlargement in the right upper quadrant may be due to disease of the liver, and in this respect carcinoma probably heads the list. The carcinoma may be primary in the liver or it may be secondary to carcinoma of the stomach. I have seen instances of an enlarged liver due to metastatic carcinoma, with no symptoms whatsoever of carcinoma of the stomach and where, because of the enlargement and in the absence of stomach symptoms, it was assumed, for the time being at least, that the patient had a tumor of the kidney.

Riedel's lobe is palpable in the renal area on the right side and is not as common as it was when the "gals" used to strive for a wasp waist and snared themselves in corsets and snared off a piece of liver. But once in a while one does

still see a case of Riedel's lobe, and it is well to bear it in mind.

In certain instances in which there is a hepatoptosis, the liver drops down and has been confused with a nephroptosis or an enlargement of the kidney. The roentgenologic evidence in a plane film plus the intravenous or retrograde urogram clears up the point.

Amebic abscess, of course, rarely is confused with a kidney lesion, but occasionally it is.

LESIONS OF THE GALLBLADDER

When the gallbladder produces a hydrops that is very large, it may be confused with a hydronephrosis. When the gallbladder contains stones that make the hydrops and at the same time the patient also has stones in the kidney, there may be a problem in differential diagnosis, not because of the enlargement of the kidney or gallbladder, but to decide which lesion demands surgical treatment first, the gallbladder or the kidney.

OTHER LESIONS

Lesions of the pancreas are occasionally confused; they are in the midline; they are carcinoma or they are pancreatic cysts. As a rule, the intravenous or retrograde pyelograms are all that are necessary and there is not much trouble in making that diagnosis.

Carcinoma of the stomach, as I have already mentioned, may be confusing at times.

Of course, in the left upper quadrant one sees lesions of the spleen, and they generally are a result of leukemia or are chronic enlargements of the spleen due to malaria. As I have said, there should be no trouble in making a differential diagnosis provided one makes a blood count, except in those cases of aleukemic leukemia where the blood count may be normal, or nearly normal.

Carcinoma of the colon on the left side occasionally is confused with a tumor of the left kidney.

Retroperitoneal tumors are occasionally confused with enlargements of the kidney. The kidney is a retroperitoneal organ and therefore it may be involved in a differential diagnosis. Most of these retroperitoneal tumors are malignant, but they may be benign.

In an occasional case one has an ovarian tumor or an ovarian cyst with a long pedicle that rests up in the right or left upper quadrant, which may at times be confused.

An illustration of what I mean by asymptomatic hydronephrosis is the following case. A young man went out to an empty lot after he came home from work and played baseball with the kids. He slid into third base, and when he got home he had a terrific hematuria, a mass in the left upper quadrant, and an x-ray showed a filling on the right side, which is normal, and nothing on the left.

What lesion of the kidney did he have that followed the sliding into third base and caused bleeding? The diagnosis must rest between a hematoma or a hematohydronephrosis, which in this case it was.

In another case a filling defect could be seen on the left side. Was it due to a tumor or a solitary cyst? It had to be one or the other. In a case of this kind one is justified, in my opinion, in operating and advising the patient that it is impossible to say whether that is a tumor or a solitary cyst. If, for example, you believe that it is a cyst, you might wait and see what happens. In this particular instance the patient had severe pain in the back and her kidney was enlarged. It was a cyst which was removed.

I wish to emphasize that the diagnosis is not always easy. I recently operated upon a Negro woman in whom I made a diagnosis of solitary cyst and tumor. It is to be remembered that when the kidney is enlarged, it may be the seat of a stone and a tumor, for instance, or a tumor and a solitary cyst, or polycystic disease of the kidney. The combination is rare, I will grant you, but it occurs. The pyelogram showed a big tumor mass; the tumor was a hypernephroma and not a hypernephroma with solitary cyst.

Once I made the diagnosis of tumor and advised a lady to be operated upon. She became very much irritated, left the hospital, and went elsewhere, where she was operated upon and they found a solitary cyst. It was with great difficulty that I tried to convince her that she was lucky to have had a cyst and not a tumor, and that nobody could ever tell the difference before operation.

In some of these enlargements, the diagnosis is neither so obvious nor so easy. One patient had an enlarged kidney, blood in the urine and pain in the back. The pyelogram was com-

patible with tumor and a diagnosis of tumor was made. Those pyelograms were made downtown in a commercial laboratory. We repeated them at the Presbyterian Hospital and they were exactly the same. In another week we made another set of pyelograms, retrograde, and had the same result. Therefore, it was perfectly obvious that this patient had a tumor with red blood cells in his urine, a kidney that was slightly enlarged, and pain in the back.

I operated upon this patient, found no tumor, found no solitary cyst, but I did open his kidney to rule out overlooking a tumor. It was difficult to understand how a man could apparently have a tumor that would make this type of pyelogram and not be able to see it. The patient had nothing wrong with that kidney.

Four months after he was operated upon I made some more pyelograms and they were normal. You tell me why. I don't know.

I had a woman patient who had an enlarged kidney and pain in the back. Because of the course of the ureter it was assumed that she had a retroperitoneal tumor. As you all know, retroperitoneal tumors make displacements in the course of the ureter. I operated upon her and found nothing. It is difficult for me to reconcile why her ureter had that peculiar shape. So, sometimes one errs, but it is better to err on the side of safety.

I was asked to see a patient who had a mass in his abdomen; they were not sure it was a kidney. It proved to be a calcified aneurysm of the aorta. The urologist does get into the department of vascular surgery once in a while.

Another case showed an interesting enlargement in the left upper quadrant. Originally there was a small tumor. It was operated upon, then recurred, was operated upon again; it was a renal osteogenic sarcoma.

Still another patient whose pyelograms were normal came in because he had a mass that was thought might be a renal tumor. The patient had a carcinoma of the stomach.

In some of these patients with kidney enlargements and kidney changes, there is bleeding. A young man went to a football game and began to bleed. It was a cold day. He was sent to a hospital and pictures were made which showed a filling defect. He came to the Presbyterian Hospital and we repeated the film. He belonged to the University of Michigan and was examined in that school's genitourinary department. They concurred in the diagnosis that he had bleeding from a probable nephritis, which was the diagnosis we made. He went home to the East, and his doctor wrote me about the films and thought the boy ought to operated on; he was bleeding again. I said to the doctor, "Swell! You're going to take his kidney out. Now what are you going to do with the other kidney when it begins to bleed?" He didn't believe that was likely to happen. He believed that the boy had a tumor. He took the kidney out. I saw the slides. They were the typical picture under the microscope of a chronic nephritis. The young man went on and developed bleeding from his other side and passed out.

Therefore, even if the kidney is enlarged, even if there is a filling defect, I think one must analyze and rationalize and not take out kidneys unnecessarily. As I say to the students, the kidney surgeon of the future will be known not by how many nephrectomies he did but how many nephrectomies he did not do.

The history in this case was perfectly obvious: rain, soaked to the skin, exposure, chill, blood in the urine. What else could it be? Nothing.

In summing up, may I say that the problems are interesting; the problems in diagnosis touch all fields of medicine, and if one will take the trouble to rejuvenate and revive the old art of a history and a physical examination it will be a lot better for the patient. As you can see, many of these lesions are diagnosable from the history and the physical examination.

COMING IN THE JANUARY, 1951 ISSUE

The Clinical Use of Histamine by Bayard T. Horton, M.D., *Mayo Clinic*

A comprehensive report of work done to date on this subject.

Treatment of Kraurosis Vulvae

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INVARIABLY associated with thickening and whitening of the vulval tegument and shrivelling of the labia is an intense pruritus. Various terms have been used to describe this condition, such as kraurosis vulvae,[1] leukoplakia vulvitis[2] and leukokraurosis.[3] Adair and Davis[4] felt that these terms were confusing and were descriptive of certain phases of the same syndrome and suggested the simple designation "chronic atrophic dermatitis of the vulva." Hunt[5] is of the opinion that the "lichen sclerosis vel atrophicus" of the dermatologist is similar to the "kraurosis vulvae" of the gynecologist. The alleviation of the intolerable irritation and annoying pruritus has proved, in the past, a most perplexing problem.

Concerning the etiology of the syndrome, little is known though much has been conjectured. It is thought to follow an avitaminosis, an estrogen deficiency or some chronic vulvovaginal infection. It is said to occur in advancing years as an abnormally regressive change in the nutritional status of the sex skin.

VITAMIN DEFICIENCIES AND KRAUROSIS VULVAE

The role of vitamin deficiency in the production of certain types of vulval dermatoses was first suggested, though somewhat naively, by Swift in 1936. In patients with lesions such as kraurosis vulvae and leukoplakic vulvitis he believed a common factor to be present and suspected that "this factor is an achlorhydria which causes a deficiency of absorption of vitamin A from the diet."[6] Independently, in the same year, Simpson and Mason advanced a new method for the treatment of senile vaginitis by the use of vitamin A in the form of cod liver oil or haliver oil orally with 100 per cent results in 30 cases. Their patients had varying degrees of chronic atrophic vaginitis. Some of them also had a distinct inflammatory reaction of the external genitalia, occasionally so severe that it gave the impression of an early leukoplakia.[7] Coincidentally, some of the individual case reports of Swift fitted into the same category as those of Simpson and Mason.

It is well established that vitamin A is an important factor in maintaining a normal structural and functional state of the vaginal epithelium of the monkey[8] and of the rat.[9] Wolback and Howe first emphasized, and this has since been confirmed by many investigators, that deficiency of vitamin A manifests itself in a metaplasia and keratinization of epithelia throughout the body.[10]

Deficiency of various B group factors has been incriminated as the responsible agent for certain types of vulvovaginitis and perigenital dermatitis. In pellagra, the butterfly dermatitis of the genital zone has long been noted.[11] Other

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The estradiol and ethinyl estradiol ointments and the pyribenzamine and antistine for oral and topical use, as well as a special cream containing pyribenzamine and estradiol, were generously supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

Aided by a grant from Ciba Pharmaceutical Products, Inc.

TABLE 1

GASTRIC TEST MEAL STUDIES

23 PATIENTS

CASE NO.	AGE	RACE	FREE HCL	TOTAL HCL	AFTER HISTAMINE	
					FREE HCL	TOTAL HCL
1	61	W	0	18	121	136
2	25	W	8	13.5	48	57
3	63	W	0	8	38	58
4	48	W	0	15	80	100
5	39	W	0	18	60	83
6	50	W	0	6	0	8
7	60	W	0	20	15	30
8	39	W				
9	60	W	0	9	0	7
10	63	W	20	30		
11	50	W				
12	50	W	15	30	80	95
13	51	W	0			
14	55	W				
15	53	W	0	5	105	130
16	74	W	0		128	140
17	54	W	0	20	15	25
18	52	W	0	6	28	48
19	31	W	4	13	52	76
20	30	W	0	4	29	37
21	38	C	0	20	40	70
22	66	W	0	20	60	90
23	43	W	0	20	17	38

investigators have intimated the specificity of these lesions by their association with other typical signs of pellagra.[12,13] In ariboflavinosis, accompanying the characteristic buccal, corneal, and tongue lesions of riboflavin deficiency, there has also occasionally been noted a dry itching dermatitis of the scrotum or vulva.[14] Dogs kept on a diet lacking in riboflavin were observed by Sebrell to develop a genital dermatitis (on the scrotum).

In 1939 Dabney claimed that nicotinic acid therapy and diets rich in vitamin B were indicated in the therapy of certain types of idiopathic pruritus vulvae.[15] Hesseltine reported a clinical study of the role of B complex factors in treatment of 22 cases of vulval dermatoses of which 15 belonged to the chronic atrophic vulvitis group; the remainder were undetermined.[16] He pointed out that the early cases of chronic atrophic dermatitis of the vulva and some of the undetermined types of vulvitis responded well to continued therapy with large doses. Although alleviation (presumable cures) transpired under the administration of factors of B complex, these conditions were not definitely classed as manifestations of deficiency diseases. More recently, Hyams and Bloom[17] have recommended the employment of massive doses of vitamin A in the treatment of leukoplakia vulvae.

Significance of the gastric test meal—The role of the gastric juices (achlorhydria or hypochlorhydria gastrica) in vulval dermatoses may or may not be open to speculation. In vitamin deficiency states it has been observed that achlorhydria is frequently present. Whether the achlorhydria is the result or the cause of the vitamin deficiency is polemical. Suffice it to say that free hydrochloric acid was found in only 4 of the 20 patients studied in this series and that all had relatively low values for total hydrochloric acid (Table 1). Such findings may be of some significance.

Foss of Cambridge performed test meals in 42 patients with kraurosis, leukoplakia, and pruritus vulvae and found that 42.8 per cent had complete achlorhydria and 35 per cent had hypochlorhydria and low total acid. He advised, therefore, as a supplement to therapy, the administration of hydrochloric acid by mouth in all patients with achlorhydria.[18] Foldes and Vajda, on the other hand, recommended large doses of vitamin A in the belief that lack of vitamin A causes atrophy of the gastric mucosa. Twenty cases of achlorhydria were treated with large doses of vitamin A for two to three weeks. In 12 cases symptoms improved, weight increased, and there was an increase of free hydrochloric acid.[19]

FIGURE 1 *(Case 1)*. Kraurosis vulvae in a white female aged 59 years.

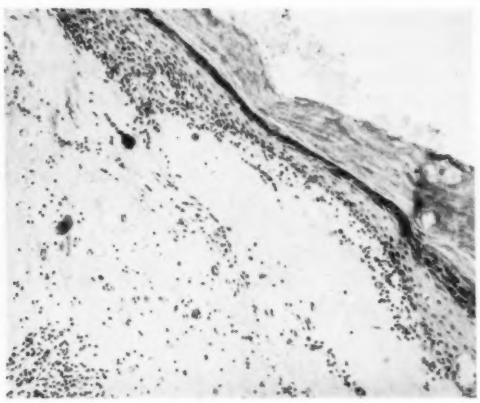


FIGURE 2 *(Case 1)*. Biopsy of vulva showing atrophy and keratinization of the epithelium, hyalinization and lymphocytic infiltration of the subepithelial tissue.

THE following case report from our series suggests a vitamin deficiency state as a possible factor in the development of kraurosis vulvae.

Case 1—S. C., a 59-year-old white woman, first presented herself at the University Hospital clinic with a perigenital dermatitis on October 5, 1937. On May 2, 1938, she was seen in the Medical Clinic and the following notation appears on the chart: "headache, vertigo, diarrhea, general formication, and pellagrous tongue." She was placed on a regimen of therapy to ameliorate the avitaminosis. On May 8, 1939, she was seen in the Endocrine Clinic and a diagnosis of pruritus vulvae, kraurosis vulvae was made (Figure 1). Vaginal smears revealed many castrate cells among many mature cells. Biopsy was taken and the pathologic report by Dr. E. R. Pund was as follows: "atrophy and keratinization of the epithelium, hyalinization and lymphocytic infiltration of the subepithelial tissue" (Figure 2).

On parenteral and local estrogen therapy the patient improved symptomatically, but recurrences of the pruritus vulvae followed discontinuation of therapy. She was seen in another clinic and surgical excision of the vulva was performed because of fear of malignancy. One year later, she again returned to the Endocrine Clinic because of a recurrence of pruritus vulvae. At this time her vaginal smear showed an estrogenic reaction and the *p*H was 4.5. She was advised to use cod liver oil locally, which she used rather periodically. The patient found that this procedure satisfactorily though not entirely alleviated the pruritus.

This patient was seen again in August, 1947, because of her pruritus and hot flashes. Kraurosis was present in the crural folds and perineum. To evaluate the effect of vitamin therapy, she was placed on vitamin A, 25,000 units twice a day, and chronic doses of vitamin B. The results were not impressive. She was then given a course of testosterone propionate, vitamin A, and dilute hydrochloric acid and an antihistaminic to use orally. The results were quite satisfactory and she remained moderately free from pruritus for two years. She was seen again in 1949 with a return of symptoms and a course of antihistaminic cream and estrogen ointment was prescribed. She again obtained satisfactory alleviation and remained practically free of pruritus until May, 1950. She was recently given a cream containing an antihistamine and estradiol with amelioration of the symptoms.

OVARIAN FUNCTION AND KRAUROSIS VULVAE

Whether kraurosis vulvae is due to an estrogen deficiency is a moot point. A deficiency of ovarian function is probably a contributing factor but not the essential cause. Women with hypo-ovarianism due to primary ovarian or pituitary failure as a rule do not have kraurosis vulvae. The vast majority of women in the menopause do not have this disorder. Moreover, it is rarely seen in the prime of a woman's life when ovarian function is normal. However, waning or altered ovarian function undoubtedly is an important factor in this condition since it is distinctly a disease of the menopausal or postmenopausal period.

The average age in Taussig's large series of cases was 49 years and in the group reported on by Adair and Davis, it was 52 years. Our patients for the greater part were in the premenopausal, menopausal, or postmenopausal period with the exception of 3 cases. Kraurosis vulvae developed in a 25-year-old surgically castrate patient six months after hysterectomy and resection of the ovaries for endometriosis. In the patient aged 30 with hypo-ovarianism, a moderate degree of

kraurosis vulvae with a localized area of leukoplakia vulvae developed several years after the onset of secondary amenorrhea. A patient, aged 31, with premature menopause presented signs of early kraurosis vulvae, and this was preceded by intense pruritus for several years during a period of functional amenorrhea. In all 3, the study of the vaginal cytology revealed the presence of castrate cells, signifying a profound estrogen deficiency. One of these cases is selected to illustrate the probable role of hypo-estrogenism as a factor in the etiology of kraurosis vulvae.

Case 2—F. H. A., a 25-year-old white woman, was first seen on March 19, 1949, because of pruritus vulvae, hot flashes, and dyspareunia. A hysterectomy and partial resection of the ovaries had been performed some six months previously for endometriosis. Examination revealed marked kraurosis of the vulva and anus with superficial ulcerations in the crural folds. A hypo-estrogenic smear was obtained on study of the vaginal cytology. Yeast-like organisms resembling *Monilia albicans* were present in the vaginal secretions. She was placed on estrogens orally, estrogenic ointment locally, propionate vaginal jelly for the yeast infection, on multivitamins and an antihistaminic p.r.n. for pruritus.

Improvement was fairly rapid. In one month's time the patient claimed 40 per cent improvement. The vaginal smear improved and the yeast-like organisms disappeared from the vaginal secretions. In four months' time healing was complete. Attacks of pruritus were so few that she took antihistaminic tablets but twice a week.

Her recovery was progressive as long as she stayed on the above medication. When antihistaminic ointment was used to replace the estrogenic ointment the relief from the pruritus was not as great. On February 11, 1950, biopsy was done and Dr. E. R. Pund reported as follows: "Slight dermal hyalinization and scattered inflammatory cell infiltrate; hyperplasia and parakeratosis of epithelium of section of perineum." The patient continues to do well and is now able to lead a normal life. Estrogens and antihistaminics, both administered orally and locally, keep her symptoms in complete abeyance.

ROLE OF INFECTIONS IN ETIOLOGY OF KRAUROSIS VULVAE

What contributory role chronic infection such as *Trichomonas vaginalis* vaginitis, mycotic vulvovaginitis, trichophytid infection and other nonspecific infections play in the causation of kraurosis vulvae is difficult to answer. Chronic vulvovaginal infections with their attendant pruritus induce trauma and local infections of the vulval tegument. Hyperkeratotic areas result from the local stress reactions to chronic irritation. Among the patients in this series there were several instances where chronic vulvovaginitis played a major role in the development of the kraurosis, for in each instance the removal of the irritating factor was followed by complete remission of symptoms and objective improvement in the condition of the vulva. The following brief case reports are presented to illustrate the possible role of vulvovaginal infections in kraurosis vulvae.

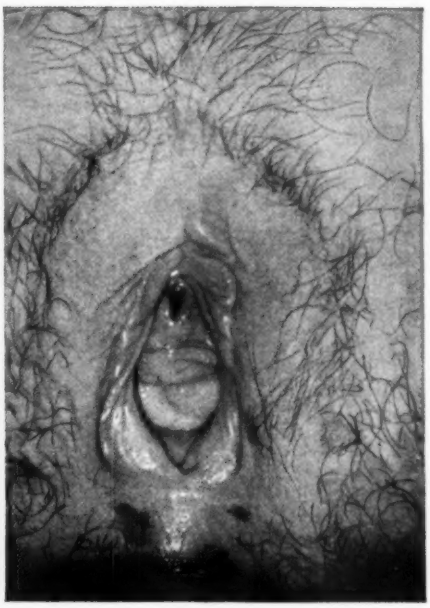
Case 3—S. C., a 64-year-old white woman, first came to the clinic in 1940 with intractable pruritus of several years' duration. Examination revealed a mild kraurosis of the vulva. Estrogens locally and orally proved of no avail. Cod liver oil locally was of little help. Nicotinic acid, vitamin B complex, and multivitamins did not alleviate the pruritus. The possibility of a local Trichophyton infection was then entertained and one-half strength Whitfield's ointment was applied. Relief was rapid and complete. The pruritus disappeared and the kraurosis lessened considerably. This patient remained symptom-free for the next seven or eight years.

Case 4—H. L. H., a 48-year-old white woman, was first seen in 1947 with a moderate degree of kraurosis and a vagina heavily infested with trichomonas. Eradication of the trichomonas was accomplished after several trials of different trichomonadicidal agents. The kraurosis improved rapidly but some pruritus remained. With the administration of estrogens locally and the help of antihistaminics the pruritus was arrested and the appearance of the vulva gradually improved. It was felt that the chronic *T. vaginalis* vaginitis was responsible for the kraurosis in this case.

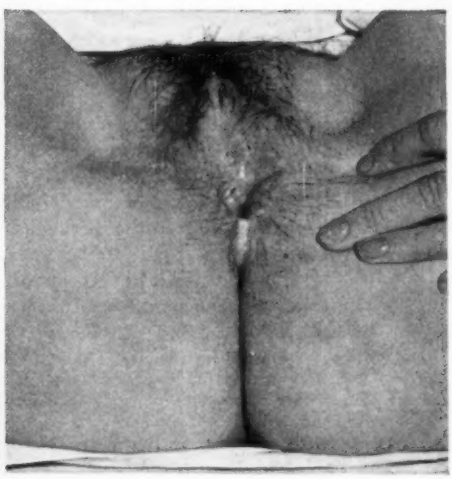
After remaining well for more than two years the patient had a recurrence of the *T. vaginalis* vaginitis. There was a severe vulval dermatosis associated with intense itching. Estrogenic as well as antihistaminic ointments proved irritating and 10 per cent zinc oxide in 1 oz. of mineral oil was applied locally as a soothing cream. She was then treated successfully for the trichomonas and is now well.

Case 5—M. W., a 39-year-old white woman with a history of removal of one ovary in 1945, was referred in January, 1950, because of intractable, intolerable pruritus vulvae. The patient had not had a night's sleep in several days and had been most uncomfortable with this affliction for several months. Her physician had treated her with estrogen orally and estrogenic ointment locally without benefit. Examination revealed multiple kraurotic areas about the vulva and anus. Vaginal secretions revealed yeast-like organisms which on culture appeared to be *M. albicans*.

The use of propionate vaginal jelly, antihistaminics orally and an estrogenic ointment topically was soon followed by the most gratifying relief. The monilial infection has long since been eradicated; nevertheless, the need for antihistaminics and estrogenic ointment continues, for mild bouts of pruritus occur when this medication is stopped. The kraurotic areas about the vulva have disappeared but the perianal lesions persist. The patient continues to use the estrogenic ointment alternating with antistine cream locally and takes an occasional antihistaminic tablet as the need arises.



FIGURES 3 and 4 *(Case 6)*. Kraurosis vulvae in a white female, age 50, before and following therapy.



FIGURES 5 and 6 *(Case 7)*. Recurrence of kraurosis vulvae in a patient who had a vulvectomy performed in 1940. Before and after therapy.

(Color plate reproduced courtesy of Ciba Pharmaceutical Products, Inc.)

EXPERIMENTAL THERAPY OF KRAUROSIS VULVAE

At first a regimen of treatment was adopted which included the oral administration of dilute hydrochloric acid, multivalent vitamins, frequently with additional massive dosage of vitamin A, estrogens in various forms, especially as a topical ointment, and cod liver oil applied locally.[20] This form of therapy was prescribed over a period of many years. We were, however, never really convinced that hydrochloric acid and vitamin therapy accomplished much other than improvement in well being and in some instances relief of indigestion. In many cases the topical application of cod liver oil and estrogenic ointments gave satisfactory though not complete relief. Estrogens orally and parenterally never seemed to equal the benefits obtained with estrogens topically.

With the advent of the antihistaminics it soon became evident that these were useful not only to alleviate allergic conditions[21] but also in the assuagement of pruritus due to dermatologic disorders.[22,23] It was decided to try various antihistaminic agents both topically and orally, alone and as adjunctive therapy. These agents proved powerful allies and enhanced the effectiveness of the estrogenic ointments in the management of kraurosis vulvae. The pruritic factor could be held in abeyance and the trauma of constant scratching could be almost entirely eliminated. Secondary infections were reduced and symptomatic improvement was often miraculous. Objectively, ulcerative lesions, leukoplakic areas seemed to disappear but in only a few instances was there restoration to normal. The use of antihistaminics with estrogenic ointment proved the main basis of therapy and provided the best results obtained in the 15 years of this investigation in the therapeusis of kraurosis vulvae.

The following case reports are presented to illustrate the management of selected cases of kraurosis vulvae.

Case 6—H. L. C., a 50-year-old white woman, was first seen on August 19, 1946, complaining of marked pruritus vulvae, hot flashes, and nocturia. Until recently, menses were fairly regular. The vaginal smear showed an estrogenic effect. Examination revealed marked kraurosis vulvae (Figure 3). A history was obtained of x-ray treatments for this condition with little benefit and rapid recurrence of the pruritus. The patient was first placed on dilute hydrochloric acid and estrogenic ointment with but slight improvement. Estrogens parenterally and multivitamins orally were added and improvement was soon marked. Occasional flare-ups occurred and on two of these occasions yeast-like organisms were found in the vaginal secretions. The yeast-like infection responded to specific therapy. On other occasions reason for the flare-ups with excoriation and cracking of the skin could not be determined. The patient was then placed on multivitamins, supplemented by 150,000 units of vitamin A per day, antihistaminics given orally and locally, and estrogenic ointment.

The results have been remarkable and at present the patient is on estrogenic ointment and antihistaminic tablets taken when itching is present. Biopsies taken from several areas on the vulva on December 10, 1949, were reported on by Dr. E. R. Pund as follows: "Hyperplasia and epidermal metaplasia of the squamous epithelium (leukoplakia). Fibrosis and some hyalinization of the subepithelial connective tissue (kraurosis); few scattered inflammatory cells. In some areas of the epithelium there is intra-epithelial anaplasia (dyskariosis)." Mild bouts of itching occur from time to time. The kraurosis seems to be held in abeyance. The lesions are smooth and are not progressive and the excoriations in the crural folds are all healed (Figure 4). The patient is perfectly content with the results of therapy. She is being watched closely at regular intervals for suspicious areas. None of these has thus far developed.

Case 7—E. H., a 60-year-old white nurse, had been complaining of pruritus vulvae for 13 years and was first seen by us on October 25, 1948. A vulvectomy had been performed in 1940 with relief for one year. Now the pruritus had become gradually worse and the patient had not had a whole night's sleep for many months. Examination revealed that the kraurosis had recurred at the site of operation (Figure 5). A biopsy was taken and reported on November 1, 1948, by Dr. E. R. Pund as follows: "Pronounced hyperkeratosis, moderate acanthosis; inflammatory cell infiltrate of subepithelial tissue, hyalinization and telangiectasis of papillary layer." The vaginal cytology showed a castrate smear.

The patient was placed on estrogenic ointment and antihistaminics orally. Relief was rapid and in one week the patient claimed 50 to 60 per cent relief and that she was now able to sleep. One antihistaminic tablet gave her relief for 24 hours at a time, the estrogenic ointment for shorter periods. She was given multivitamins and dilute hydrochloric acid with her meals and her digestion improved. After one month of therapy there was over 95 per cent clinical improvement (Figure 6). The estrogenic ointment was replaced by antihistaminic cream, and 100,000 units of vitamin A per day were added. She found that greater relief was obtained from the estrogenic ointment than the antihistaminic cream.

Objectively, the improvement in the kraurotic zones was slow. Her vitamin A intake was then further increased to 250,000 units per day along with estrogen ointment and multivitamins orally and when she returned one month later she stated the results were excellent. She took only 7 antihistaminic tablets during the month for relief of mild pruritic attacks. She remained on therapy with excellent results. She returned three months later with an exacerbation of pruritus and redness of the vulval area. Yeast-like organisms

resembling monilia were found in the vaginal secretions. Attention was paid to this complication but the rawness of the vulval dermatosis persisted. Local ointments proved irritating. Bichloride of mercury washes (1:2,000) helped considerably and the patient improved rapidly. She remains on antihistaminics orally and estrogenic ointments locally with almost complete abatement of symptoms.

DISCUSSION

Of the many dermatoses affecting the vulva, the diagnosis of kraurosis vulvae carries with it the most sinister connotation. Epithelioma of the vulva does follow in old chronic cases. It is felt that it is not the kraurosis or the leukoplakic vulvitis but the constant trauma that is the predisposing factor in the development of malignancy. If the pruritus could be kept at a minimum thereby eliminating the constant scratching, irritation, infection, and reinfection, epithelioma should rarely follow.

Of the 23 cases comprising this series several have been observed over a period of 10 years or longer. In none has epithelioma developed. Biopsies have been performed whenever further investigation was warranted.

In the therapy of intractable pruritus, consideration should be given to many underlying factors such as vulval infections, vaginal infestations, and vitamin deficiencies. The topical application of ointments frequently causes further irritation, especially if applied to raw, denuded surfaces. In such instances it is best to use soothing ointments first, such as 10 per cent zinc oxide in mineral oil. If an impetiginous vulval dermatitis is present, washes with 1:2,000 solution of bichloride of mercury are recommended.

The use of estrogenic ointments such as estradiol or ethinyl estradiol is of inestimable value. There may be a delay of several weeks before the full benefit of local estrogenic therapy makes itself felt. One annoying complication due to estrogen therapy is the frequent occurrence of yeast-like infections in the vagina due to glycogen deposition in the vaginal mucosa and the increased acidity of the vaginal secretions. Instillations with vaginal propionate jelly will, in most instances, readily rid the patient of the yeast infection, and alkaline (soda) douches may be used at this time to hasten the result and prevent recurrences.

The use of antihistaminic cream to instantly allay the pruritus has been most gratifying. Occasionally, patients are found to be sensitive to these antihistaminic ointments, especially if raw, cracked, or ulcerated areas are present. The oral administration of antihistaminics is a most valuable adjunct to therapy and will usually within a few minutes allay for several hours or even days the pruritus of kraurosis vulvae. Not all patients respond in similar fashion to the same antihistaminic agent and whereas one drug may be found wanting, another will prove satisfactory. The antihistaminic of choice will vary with different patients.

Dilute hydrochloric acid, vitamin A, or cod liver oil orally may be used empirically. The cod liver oil locally often proves soothing and healing.

It is felt that though kraurosis vulvae may be completely arrested and the vulva restored to normal in the early cases, the lesions of long duration are irreversible. Nevertheless, progressive deterioration and carcinomatous changes will probably not occur so long as the patient is kept free from severe pruritus and the constant trauma that attends it. Surgical interference, i.e., vulvectomy, is unnecessary if proper therapy is instituted early in the disease. In only one patient in this series was vulvectomy recommended because histologic examination of biopsy tissue from a leukoplakic area revealed an area suggestive of intra-epithelial anaplasia (Figure 7). No evidence of malignancy was found on histopathologic study of the vulva. In 2 other instances, vulvectomy was performed at other clinics because of intractable pruritus. In each instance the signs and symptoms returned at the site of the operative scar or in the crural folds and perineal areas.

CONCLUSIONS

1. Kraurosis vulvae may be associated with or follow a chronic vulvovaginal infection, an avitaminosis, or an estrogen deficiency. The actual etiology of kraurosis vulvae is still unknown.

2. Carcinomatous degeneration will not, it is believed, follow in the early cases of kraurosis vulvae if the pruritus is kept under control, thus avoiding any constant trauma, irritation, and infections.

3. Of greatest value in allaying pruritus is the topical application of antihistaminics and estrogenic ointments. The oral administration of antihistaminics is a most valuable adjunct to local

FIGURE 7 *(Case 10)*. Biopsy of leukoplakic area of vulva in patient 63 years of age revealing area suggestive of early intra-epithelial anaplasia. Conservative management of this case was not attempted and vulvectomy was performed.

therapy. Antihistaminic or estrogenic ointments may aggravate the vulval dermatitis if denuded or ulcerated areas are present. In such instances soothing ointments should first be employed in association with oral antihistaminics and estrogen therapy.

4. The administration of dilute hydrochloric acid, cod liver oil, vitamin A, vitamin B complex, may be used empirically.

5. The therapy of complicating factors of vulvovaginal infections such as intertriginous dermatitis, trichomoniasis, moniliasis, and trichophyton infections should not be overlooked. Signs of avitaminosis should be sought for. Estrogen deficiency states should be adequately treated.

6. Radical measures such as vulvectomy are unnecessary in those patients in whom the pruritus is kept well under control and who are kept under close scrutiny with biopsies performed when necessary.

7. The physical discomfort of kraurosis vulvae, so frequently augmented by mental disquietude and insomnia, may be ameliorated by the combined use of antihistaminics and estrogens topically and orally.

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Terminal Ileum Duplex

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An abnormality of the terminal portion of ileum which may be responsible for symptoms similar to those of other conditions frequently may be encountered at operation but has not received attention in the literature from anatomists or surgeons. The anomaly consists of a "kinking" of the small bowel caused, apparently, by a shortening or constriction of the posterior peritoneum as it reflects onto the mesentery of the ileum. The result is a doubling, or duplex, of a section of the terminal small bowel which I have called *terminal ileum duplex* and some of my associates have described as the "McGregor kink."

The drawings in Figure 1 illustrate the progressive development of ileum duplex and the steps necessary in the surgical repair of the condition. One may visualize the posterior peritoneum as it reflects upward onto the mesentery of the small bowel and it is apparent that with a shortening of the peritoneum a section of the bowel would be drawn downward, forming a "U" (Figure 1a). In subsequent stages (Figure 1b, c, d) the duplex becomes "V" shaped until it is complete and obstruction is acute.

The cause of ileum duplex is unknown but the condition may result from a previous terminal ileitis, an adenitis or a general peritonitis from an earlier attack of appendicitis or pelvic inflammatory disease. It seems more logical and reasonable to believe that ileum duplex is the end result of a developmental anomaly, for the condition is found in all degrees without accompanying findings, such as adhesions, which the surgeon observes at times following a general case of peritonitis.

During the past five years ileum duplex has been encountered in 37 cases by the author and surgical elimination of the condition has been followed by complete remission of all symptoms in every instance. The frequent occurrence of ileum duplex indicates that it should be considered a possibility in making provisional diagnoses and in exploratory operations on the abdomen. Definitive characteristics of each case are given in Table 1.

SYMPTOMS

Patients with ileum duplex give histories of pain and distress for weeks or months, with symptoms of indigestion such as eructations of gas, heartburn, water brash, simulating or suggestive of peptic ulcer, without relief from antacid preparations or medications. Lower abdominal pain, chiefly referred to the right lower quadrant, is sometimes accompanied by nausea and vomiting, minor at first but gradually increasing in severity. Frequently, patients have been operated upon with a provisional diagnosis of appendicitis but removal of an acute or chronic appendix has not provided relief of their discomfort.

Patients describe the pain as "cramp-like" in character, or suggestive of acute intestinal obstruction. When interrogated, the patient states that the pain comes on gradually and usually is not related to meals, but close questioning will elicit the information that the pain or the cramp-like sensation occurs five to six hours after the ingestion of some food or fluid. The pain reaches maximum severity, then gradually subsides,

DOUGLAS U. McGREGOR

followed by freedom from all symptoms for several hours.

Application of heat to the abdomen is not of value and the majority of these patients become nauseated and may vomit. Their attempts to relieve their symptoms or sensations with an enema produce unsatisfactory results. Some roll over in bed seeking comfort, assuming the knee-chest position. In some, but not usually, the pulse and temperature may be slightly elevated, with an increase in white blood cells. The history may record a definite loss of appetite, owing especially to the individual's fear of pain from taking food. Urination or bowel habits are seldom altered and blood is not evident in the stools.

DIAGNOSIS

Ileum duplex is usually found in the terminal section of the ileum, approximately 3 to 20 inches from the ileocecal valve. When normal peristalsis is passing the food bolus along the small bowel, an interruption occurs at the point of partial or complete obstruction, producing a "delay" in peristaltic movement, with pain or distress resulting for the patient. This phenomenon of delayed peristalsis as the wave advances toward the apex of the duplex may be observed directly by the surgeon.

In diagnosing ileum duplex the case history is important, with careful consideration of the periodicity of distress throughout the 24-hour period. Normally, ingested food reaches the terminal ileum approximately six to eight hours after entering the stomach, provided no obstruction is encountered in the intestine. It is easy to visualize peristalsis in the small bowel moving the food residue along to the point of semi-obstruction—the apex of the duplex—where it is blocked. The resulting pain persists until the contents of the bowel eventually have been forced past the area of obstruction, after which a period of relief from distress ensues.

Radiologic examination may be of tremendous assistance in establishing a preoperative diagnosis of ileum duplex. If the radiologist is forewarned of this possibility he may, by closely following the progress of a barium meal, observe a retarded passage through the small bowel and verify the suspected delay in emptying of the terminal ileum. In one of the cases reported (9) a delay of 120 hours occurred in the passing of barium through the last six inches of the small bowel (Figure 2), although a film showed the first portion had reached that point two hours after ingestion of the meal. The preoperative diagnosis of ileum duplex was confirmed at operation. In another case (10) radiologic examination showed an obstruction of the terminal ileum 48 hours after ingestion of a barium meal, and the diagnosis of ileum duplex also was verified at operation.

Ileum duplex must be differentiated from acute appendicitis, mesenteric adenitis, acute obstruction and Meckel's diverticulum. Of these, undoubtedly the most commonly mistaken diagnosis is that of acute or chronic appendicitis. In patients who previously have undergone appendectomy without relief of symptoms, careful history and physical examination, accompanied by x-ray studies considering the normal temperature, the normal pulse rate and the normal white blood count, may provide the basis for a diagnosis of ileum duplex even though tenderness is found over the right lower half of the abdomen, at times extending to the midline and even to the left side. Rectal examination is negative. The tenderness in the abdomen may be absent at periods in the day when the terminal portion of the small intestine is empty.

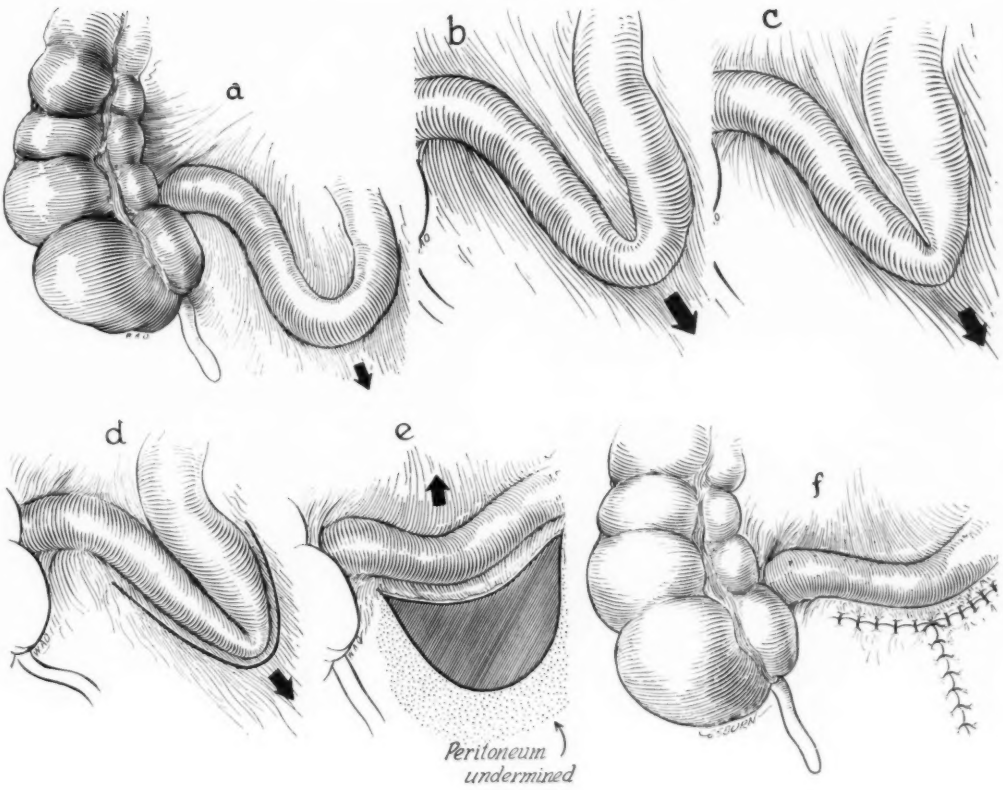

FIGURE 1*a*. Ileum duplex 1+, or duplex minor. The ileum assuming a "U" shape as it is drawn downward.

b. Ileum duplex 2+, or duplex moderate. The "U" forming a "V."

c. The "V" is more pronounced and causing partial obstruction.

d. Ileum duplex 4+, or duplex complete. The apex of the acute angle formed by the bowel produces obstruction. Line of incision necessary to relieve obstruction is shown.

e. The ileum has been straightened, leaving the denuded area (oblique lines). Undermining of the posterior peritoneum allows approximation.

f. Obstruction relieved and peritoneum closed. Appendix is removed routinely.

Ileum duplex is found in patients of both sexes at all stages in life, but seems to occur more frequently in the third and fourth decades. Among the cases presented in Table 1 were three members of the same family, all between 20 and 30 years old. Case 23 had previously had an appendectomy. In cases 17 and 25 the provisional diagnoses were "acute appendicitis" but at operation normal appendices were found. In each of the three patients a duplex 3+ was corrected, with complete relief subsequently.

THE following abstracts of case histories are typical of ileum duplex and demonstrate the need for consideration of this possibility in making provisional diagnoses and in the performance of abdominal surgery.

CASE REPORTS

Case 36—A man 42 years old was first seen with a complaint of distress in the lower right portion of the abdomen which had persisted for two years, gradually increasing in severity and accompanied by nausea and

TABLE 1

DATA FROM MEDICAL AND SURGICAL RECORDS OF 37 CASES OF ILEUM DUPLEX DEMONSTRATING MAJOR FACTORS IN DIAGNOSIS AND SURGICAL REPAIR OF THE ANOMALY

CASE NO. (SEX AND AGE)	PREVIOUS OPERATIONS	SYMPTOMS						X-RAY FINDINGS	PROVISIONAL DIAGNOSIS	ILEUM DUPLEX		PATHOLOGY
		NAUSEA	VOMITING	WHITE BLOOD CELLS	WEIGHT LOST	TEMPERATURE	PULSE			DEGREE	DISTANCE FROM VALVE, INCHES	
1 (F 37)	Rectovaginal fistula	No	No		Yes	99.1	78		Duplex	3+	5	Chronic appendicitis
2 (M 23)	?	Yes	Yes	15,100	No	101	80		Acute appendicitis	1+	6	Acute appendicitis
3 (M 47)	Appendectomy	Yes	Yes	6,600	Yes	98.2	76	Negative	Obstruction	1+	6	Negative
4 (M 34)	None	Yes	Yes	16,000	No	99	60		Family insistence	1+	4	Normal appendix
5 (M 36)	None	No	No	Not done	No	98.3	74		Appendicitis	3+	3	Catarrhal appendix
6 (F 54)	Hysterectomy Appendectomy	Yes	Yes	15,400	No	100	82		Obstruction	3+	5	Obstruction
7 (F 15)	None	Yes	Yes	Not done	No	99	88		Appendicitis	1+	6	Normal appendix
8 (F 22)	None	Yes	Yes	12,400		99.2	96		Mesentery glands	1+	7	Normal appendix
9 (F 36)	Appendectomy	Yes	Yes	10,800	No	98.2	88	Duplex	Duplex	2+	10	
10 (F 28)	None	Yes	No	Not done		100	88	Duplex	Duplex	1+	8	Normal appendix
11 (M 55)	Herniotomy Appendectomy	Yes	Yes		Yes	98.2	66	Duodenal ulcer	Possible peritonitis and peptic ulcer	2+	10	
12 (M 64)	None	Yes	Yes	6,600		98.1	76	Cholelithiasis	Cholecystitis	3+	6	Fibrous appendix, chronic inflammatory cholecystitis
13 (F 29)	None	Yes	Yes	9,800 13,400	No	98.4	84		Appendicitis	2+	3	Normal appendix
14 (F 36)	Pelvic	Yes	Yes	6,150	Yes	98.4	68	Stomach and colon negative	Dystrophy	2+	5	Normal appendix
15 (F 42)	None	Yes	No	Not done	No	98.1	84		Obstruction	4+	12	Chronic fibrous appendix
16 (F 54)	None	Yes	Yes	11,400 15,800		100	92		Appendicitis	3+	12	Catarrhal appendix
17 (F 15)	None	Yes	Yes	13,200	No	99	100		Appendicitis	3+	6	Subacute appendix
18 (F 30)	None	Yes	Yes	14,700	No	99.4	86		Appendicitis	3+	8	Catarrhal appendix
19 (M 52)	None	Yes	Yes	10,000	No	98.3	88		Appendicitis	3+	14	Normal appendix
20 (F 24)	None	Yes	Yes	Not done	No	97.2	60		Appendicitis	3+	8	Normal appendix and ovarian cyst
21 (M 35)	Cholecystectomy Appendectomy	Yes	Yes	10,000	Yes	98.4	80	Regional ileitis	Regional ileitis	4+	16	
22 (F 21)	None	Yes	No	Not done		98	88		Chronic appendicitis	3+	8	Normal appendix
23 (F 25)	Appendectomy	Yes	Yes	7,600	No	97	88	Negative	Duplex	3+	8	
24 (M 44)	None	Yes	Yes	11,000	No	99.2	90		Acute appendicitis	2+	10	Catarrhal appendix
25 (M 23)	None	Yes	Yes	7,800	No	99.2	90		Appendicitis	3+	8	Normal appendix
26 (F 45)	Right nephrectomy Appendectomy	Yes	No	5,700	No	97.2	78		Possible duplex	1+	6	
27 (M 25)	None	No	No	Not done	No	99.2	68		Chronic appendicitis	2+	8	Chronic appendix
28 (M 27)	None	Yes	Yes	14,600	No	99	92		Appendicitis	3+	8	Catarrhal appendix
29 (M 34)	None	Yes	Yes	14,600	No	99.3	88		Obstruction	3+	10	Normal appendix
30 (F 29)	None	No	No	9,400	Yes	98.4	118		Dysmenorrhea	1+	8	Fibrous appendix
31 (F 34)	Hysterectomy Appendectomy	Yes	Yes	Not done	No	98.2	88		Possible duplex	4+	8	Chronic cervicitis
32 (M 40)	None	No	No	4,800	Yes	97.4	72		Appendicitis	3+	8	Fibrous appendix
33 (M 62)	None	Yes	Yes	14,800 8,000	No	98	78	Diverticulitis	Diverticulitis	4+	6	Normal appendix
34 (M 29)	None	Yes	Yes	7,600	No	97	64		Appendicitis	2+	4	Catarrhal appendix
35 (M 22)	None	Yes	No	Not done	No	102	96		Acute appendicitis	1+	3	Normal appendix
36 (M 42)	Appendectomy	Yes	Yes	Varying	No	Varying	Varying	Negative (delay in emptying terminal ileum)	Obstruction	4+	8	
37 (M 34)	Appendectomy	Yes	Yes	Not done	No				Obstruction	4+	8	

FIGURE 2. Barium remaining in terminal ileum 120 hours after ingestion (Case 9).

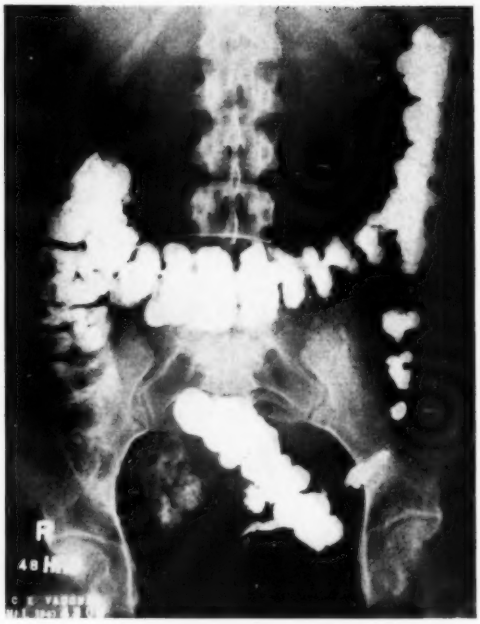

FIGURE 3. Obstruction of terminal ileum shown by barium meal 48 hours after ingestion (Case 10).

vomiting. The pain was most severe about 2:00 A.M. following ingestion of a heavy meal some seven hours previously.

The patient gave a history of an appendectomy when 25 years old. Complete physical examination with intensive gastrointestinal x-ray studies which had been completed at different centers were persistently negative, with one exception, that of evidence of delay in the emptying of the terminal ileum.

Surgical exploration of the abdomen was negative except for a duplex 4+, approximately eight inches from the ileocecal valve. Relief of the duplex and repair of the posterior peritoneum were followed by freedom from pain or distress for the past five years.

Case 37—A man 34 years old gave a history of acute abdominal pain at various intervals. The diagnosis was acute appendicitis, and after repeated attacks his appendix was removed in 1922. The symptoms were relieved for approximately two weeks before pain, similar to that originally complained of, recurred. The pain increased in severity, occurring at definite intervals, approximately six to seven hours after ingestion of each meal. The pain eventually lasted as long as one-half hour and was accompanied by nausea and vomiting.

Operation in 1947 revealed a duplex 4+ which was repaired with subsequent relief of all symptoms.

Case 20—A woman 24 years old was admitted to the hospital with acute lower abdominal distress, elevated temperature, increased pulse rate, and increased white blood cell count. Provisional diagnosis was acute appendicitis. Exploration of the abdomen showed the appendix to be lateral to the cecum, bound upward toward the liver. The cecum was semi-rotated so that the ileocecal valve entered the right side of the colon, the small bowel passing behind the lower portion of the cecum, doubling back and being held down by the lateral peritoneal wall, in what is typical of a reverse ileum duplex. Dissection within the area to approximately five inches from the ileocecal valve permitted turning the cecum into normal position, and with separation of the lateral and posterior peritoneum, a modified Waugh coloplexy was undertaken. The appendix appeared normal but a large right ovarian cyst was found which contained chocolate-colored material and other findings were typical of endometriosis. With correction of the duplex 3+ all symptoms subsided.

Case 21—A man 35 years old gave a history of a cholecystectomy several years earlier and of an appendectomy only two years prior to admission to the hospital; he complained of acute abdominal distress, chiefly confined to the lower right portion of the abdomen. Serial gastrointestinal study provided a radiologic diagnosis of regional ileitis, most marked in approximately eight inches of the terminal ileum proximal to the cecum. This section was described as being narrowed. With this radiologic diagnosis, the history, and abdominal examination verifying the ten-

derness in the lower portion of the abdomen, the provisional diagnosis was regional ileitis.

Upon exploration of the abdomen the terminal ileum appeared to be quite normal but a duplex 4+ was found approximately 16 inches from the ileocecal valve, which could account for the radiologist's impression that there was a retardation from a regional ileitis. A small inguinal hernia was repaired in addition to correction of the duplex and the patient's convalescence was uneventful with relief of all symptoms.

SURGICAL PROCEDURE

Preoperative care—Complete physical examination and any necessary dental care usually advocated before elective surgery, should be recommended. Upon admission to the hospital complete laboratory examinations of blood, urine and stools should be ordered. The patient should receive a high-calorie, high-protein, liquid diet. Laxatives of choice are given until the entire bowel is free of fecal contents.

Abdominal preparation of choice is prescribed for the day of operation. Preoperative sedation is ordered according to the anesthetist's instructions. Preferably, surgery is undertaken with spinal anesthesia, which produces a quiescent abdomen for exploratory purposes, eliminating unnecessary packing or manipulation of the bowel.

Technic—Repair of the ileum duplex is accomplished as shown in Figure 1 (d, e, f). With a preoperative diagnosis of acute or chronic appendicitis, or possible duplex, in exploring the abdomen the surgeon may find an appendix which appears normal. Under these conditions careful inspection of the terminal portion of the ileum may reveal a semi-kinking or complete kinking of the small bowel. Further exploration will probably expose the shortening of the posterior peritoneum, described earlier, in which definite bands of this peritoneum are pulling down on the mesentery of the ileum. When the tension is released and the bowel brought upward and forward an area is left denuded, that may extend down along the iliac muscle. To provide the required covering it may be necessary to strip the peritoneum on both sides, laterally and inwardly, so that this posterior peritoneum may be brought over the unprotected area. Care must be exercised to avoid interference with the blood supply to the small bowel. Without very good visualization, inadvertent destruction of these vessels is very likely.

After reconstruction of the posterior peritoneum and mesenteric area and removal of the appendix, if present, drainage was not necessary in any of the cases reported. Chemotherapy may be used at the discretion of the surgeon.

Postoperative care—Postoperative care may be routine hospital procedure, with fluids and diet as tolerated by the patient. Sedation should be minimal to avoid any interference with the peristaltic movements of the small intestine. Ambulation the first or second day after operation is advocated.

SUMMARY

An abnormality of the terminal ileum is described which has not been reported in the literature and frequently has been overlooked at time of operation, or considered insignificant. Cases are presented in which terminal ileum duplex was found in varying severity.

Terminal ileum duplex is found in men and women of all ages, more frequently in patients between 20 and 40 years old.

The condition is characterized by pain produced by interference with peristaltic action in the ileum and may develop to the extent of producing complete obstruction.

Ileum duplex may be diagnosed preoperatively and surgical repair definitely will relieve the abdominal symptoms it produces.

DR. BLADES NAMED TO VA ADVISORY GROUP

Dr. Brian B. Blades, professor of surgery at George Washington University and chief consultant in thoracic surgery for the Veterans Administration, has been appointed to the VA's Special Medical Advisory Group. Dr. Blades is a member of *Postgraduate Medicine's* Specialty Advisory Board.

Dr. Charles W. Mayo, Mayo Clinic, Rochester, Minnesota, is chairman of the advisory group.

In addition to his duties at George Washington University and as a chief consultant for VA, Dr. Blades is chief of surgery at the George Washington University Hospital and consulting surgeon at VA's Mount Alto Hospital.

CLINICAL STUDY

Clinical Safety of Polysorb

A NEW HYDROPHILIC ABSORPTION BASE

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It is generally recognized that there is no universal ointment base and that for optimum effects, the base must conform to the needs of the patient as well as be a suitable vehicle for the medicaments incorporated. The problem of the proper formulation of the ointment prescription becomes readily recognizable when one considers the properties of the available ointment bases.

The superiority of the emulsified base is rather well known and both the water-in-oil and the oil-in-water bases have established their places in dermatology. However, the water-in-oil emulsion enjoys many advantages not found in the other type of base. The water-in-oil base, because of its continuous oil phase, provides a direct contact with the surface lipids of the skin. The continuous oil phase, moreover, acts as a protective covering for the treatment area in contrast to the oil-in-water base in which there is a weakening of this desirable property due to the presence of an external aqueous phase. The oil-in-water bases dry out, resulting in a deposition of fatty materials and a concentration of active ingredients.

The emulsified bases are all prepared with a surface active agent, which may be either anionic, cationic or nonionic. While numerous pharmaceutical incompatibilities have been reported[1-4] for these bases, the clinician is primarily concerned with the irritating and sensitizing properties of the vehicle. Many of the surface active agents used to prepare emulsions have been found to be irritating to the skin and mucous membranes.[5] Lane and Blank[6] suggested that the irritation may be due to an alkalinity or the ability of these substances to penetrate skin or a combination of these factors. Roy and Blank[7] obtained a high percentage of positive patch tests to triethanolamine soaps and Ellis[8] reported the sensitizing action of aquaphor and other cholesterol-containing bases. Sulzberger and Morse[9] and also Fanburg[10] reported the sensitivities to wool fat and cholesterol bases.

POLYSORB, a new hydrophilic absorption ointment base, consisting of sorbitan sesquioleate in a wax-petrolatum mixture, is of neutral *p*H and capable of absorbing 8 to 10 times its weight of water. It spreads easily and smoothly over both dry and moist skin. Its pharmaceutical compatibilities[11] and stability indicate that it is an extremely desirable base. It was of interest to evaluate the clinical safety of this base in order to ascertain its scope in dermatologic practice. This report is only a study of the possible irritating and sensitizing aspects of the base and its therapeutic uses will be reported at a later date.

EXPERIMENTAL

Rabbit eye irritation tests—Polysorb was studied as the anhydrous base and in its hydrated form at one-fourth, one-half and three-fourths saturation levels. The test mixture was placed in the conjunctival sacs of the rabbit's eyes and observations were made over a period of 36 hours for signs of irritation. There was no evidence of hyperemia or clouding of the cornea with any of the test mixtures studied.

Rabbit skin tests—The abdomen of the test animal was shaved and an area 6 by 10 cm. delineated into 10 sections, each 2 by 3 cm. The test material was applied to each alternate section with a wooden applicator stick and covered with sterile gauze. The test areas were examined periodically for three days for signs of irritation. Rabbit skin is generally more sensitive to various agents than is human skin and the presence of a hyperemic reaction may result with materials that are apparently inert to human skin.[5] Since alternate sections of the test area were

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TABLE 1

RABBIT SKIN IRRITATION OF POLYSORB AND DRUG POLYSORB MIXTURES*

TEST AGENT	PER CENT CONCENTRATION
Polysorb (anhydrous)	
Polysorb (one-fourth saturation)	
Polysorb (one-half saturation)	
Polysorb (three-fourths saturation)	
Polysorb (saturated)	
1. Acriflavine	1
2. Atropine sulfate	0.5
3. Balsam of Peru	5
4. Benzoic acid	5
5. Benzocaine	5
6. Boric acid solution	10
7. Burow's solution	10
8. Calamine	17
9. Calomel	30
10. Camphor	5
11. Cetyl pyridinium chlorine	1
12. Coal tar	5
13. Cod liver oil	20
14. Gentian violet	1
15. Glycerin	10
16. Hydrogen peroxide	3
17. Iodine	2
18. Iodoform	5
19. Lead subacetate solution	10
20. Liquor carbonis detergens	5
21. Mercury oxide	5
22. Merthiolate	1 (1:5000)
23. Phenol	4
24. Pine tar	5
25. Potassium sulfurated	4
26. Potassium iodide	5
27. Resorcinol	6
28. Salicylic acid	5
29. Silver proteinate	2
30. Sodium sulfathiazole	10
31. Sodium sulfadiazine	10
32. Sulfur	15
33. Tannic acid	10
34. Undecylenic acid	20
35. Whitfield's ointment	50
36. Zinc oxide	20
37. Zinc peroxide	5
38. Zinc undecylenate	20

*No signs of sensitization or irritation were observed in any of the test animals during the first three days; after resting the animals for five days following completion of the first determination, the experiment was repeated to exclude any possible sensitization that may have developed; no sensitization or irritation was observed.

used, the intervening portion served as a control. In this manner differences in reaction from one animal to another were ruled out. The anhydrous base and hydrated base as well as drug base mixtures were studied (Table 1). After resting the animals for five days following the completion of the first determination, the experiment was repeated in order to exclude any possible sensitization that may have developed (Table 1).

Human skin testing—Skin patch testing was carried out on more than 100 subjects using the general technic described by Schwartz. The subjects

TABLE 2

HUMAN SKIN PATCH TESTING OF POLYSORB AND DRUG POLYSORB MIXTURES*

AGENT	PER CENT CONCENTRATION
Polysorb (anhydrous)	
Polysorb (one-fourth saturation)	
Polysorb (one-half saturation)	
Polysorb (saturated)	
1. Atropine sulfate	0.5
2. Balsam of Peru	5
3. Benzocaine	5
4. Burow's solution	10
5. Calomel	30
6. Camphor	5
7. Cetyl pyridinium chlorine	1
8. Coal tar	5
9. Hydrogen peroxide	3
10. Iodine	2
11. Iodoform	5
12. Liquor carbonis detergens	5
13. Phenol	4
14. Pine tar	5
15. Resorcinol	6
16. Silver proteinate	2
17. Sodium sulfathiazole	10
18. Tannic acid	10
19. Undecylenic acid	20
20. Zinc peroxide	5

*No evidence of any irritation or sensitivity was noted in the first series of 100 subjects tested. A second group of 50 patients with specific allergies was patch tested as described, and showed no sensitization or irritation.

were chosen at random and consisted of 47 females with an age range of 19 to 53 years and 62 males with an age range of 17 to 47 years. The subjects were instructed not to bathe or otherwise interfere with the test area during the course of the testing. The results of this study are reported in Table 2. Both the free-base and drug-base mixtures were used. There was no evidence of any irritation or sensitivity occurring in the course of the patch testing, in contrast to the rather well known difficulties observed with some of these drugs.

The effects of the base and drug-base mixtures were studied on patients with known allergic histories. A group of 50 patients with specific allergies was selected and patch tested in the manner already described (Table 2).

Since medication is primarily intended for use on pathologic skin which, presumably, might react in a manner different from normal skin, patch testing was carried out on a group of patients with dermatoses. This phase of the study also included the base and drug-base mixtures and is reported in Table 3. It is of interest to note that in the course of the treatment of the different dermatoses with drug-Polysorb mixtures in more than 200 patients, no instance of sensitization or irritation was observed. In many cases large quantities of medication were employed for some time. The therapeutic efficiency of Polysorb will be reported at a later date.

TABLE 3

PATCH TESTING OF PATIENTS WITH DERMATOSES*

CASE *(Sex, Age)*	DIAGNOSIS *(Duration)*	CASE *(Sex, Age)*	DIAGNOSIS *(Duration)*
1 (M 33)	Acrosclerosis sellei (8 months)	57 (M 26)	Pityriasis rosea (2 weeks)
2 (M 54)	Impetigo (2 weeks)	58 (F 32)	Lupus erythematosus (2 years)
3 (M 39)	Erythema multiforme (1 month)	59 (F 26)	Lupus erythematosus (6 months)
4 (M 31)	Neurodermatitis (1 month)	60 (F 28)	Disseminated neurodermatitis (2 years)
5 (M 27)	Dermatophytosis (3 weeks)	61 (F 25)	Disseminated neurodermatitis (5 years)
8 (M 35)	Urticaria (1 month)	62 (F 60)	Neurotic excoriations (2 years)
9 (M 30)	Infectious eczematoid dermatitis (9 months)	63 (F 48)	Neurotic excoriations (4 years)
10 (M 63)	Basal cell carcinoma (1 year)	64 (F 16)	Acne vulgaris (3 years)
11 (M 21)	Hemangioma (4 years)	65 (F 22)	Acne vulgaris (4 years)
14 (M 39)	Disseminated lupus erythematosus (1 year)	66 (F 15)	Acne vulgaris (3 years)
15 (M 63)	Pediculosis corporis (6 months)	67 (F 16)	Acne vulgaris (2 years)
16 (M 26)	Urticaria (2 months)	68 (F 33)	Pruritus vulvae (6 months)
18 (M 33)	Purpura (1 year)	69 (F 58)	Varicose ulcer (2 years)
24 (M 26)	Urticaria (1 year)	70 (F 63)	Varicose eczema (4 years)
27 (M 24)	Contact dermatitis (1 month)	71 (F 34)	Bacteride, feet (2 years)
28 (M 54)	Taboparesis (3 years)	72 (F 36)	Bacteride, feet (1 year)
29 (M 44)	Lupus erythematosus (6 years)	73 (F 60)	Seborrheic dermatitis (6 years)
30 (M 27)	Hydroa vacciniforme (4 years)	74 (F 23)	Psoriasis (2 years)
31 (M 45)	Exfoliative dermatitis (1 month)	75 (F 32)	Psoriasis (15 years)
32 (M 25)	Neurodermatitis (18 months)	76 (F 35)	Psoriasis (10 years)
33 (M 50)	Infectious eczematoid dermatitis (2 months)	77 (F 33)	Atopic eczema (30 years)
34 (M 53)	Dermatophytosis (1 month)	78 (M 32)	Oil dermatitis (6 months)
35 (M 26)	Hypostatic dermatitis (6 months)	79 (M 23)	Dermatitis venenata, rhus (2 weeks)
36 (M 43)	Blastomycosis (1 year)	80 (F 14)	Dermatitis venenata, rhus (1 week)
37 (M 76)	Basal cell carcinoma (1 year)	81 (F 9)	Dermatitis venenata, rhus (3 days)
38 (M 78)	Varicose ulcer (2 years)	82 (M 60)	Seborrheic dermatitis (6 months)
39 (M 18)	Erythema multiforme (2 months)	83 (M 28)	Seborrheic dermatitis (2 years)
40 (M 38)	Infectious eczematoid dermatitis (6 months)	84 (M 32)	Sycosis vulgaris (6 months)
41 (M 56)	Varicose ulcer (3 months)	85 (M 42)	Sycosis vulgaris (1 year)
42 (M 28)	Lichen planus (5 months)	86 (F 52)	Pruritus vulvae (5 years)
43 (M 26)	Psoriasis (3 years)	87 (F 48)	Pruritus vulvae (2 years)
44 (M 26)	Psoriasis (6 years)	88 (M 26)	Atopic eczema (25 years)
45 (M 29)	Atopic eczema (20 years)	89 (M 28)	Atopic eczema (23 years)
46 (M 26)	Atopic eczema (6 years)	90 (F 33)	Herpes zoster (2 days)
47 (M 41)	Scleroderma (3 years)	91 (M 48)	Herpes zoster (1 week)
48 (M 28)	Seborrheic dermatitis (1 year)	92 (M 42)	Lichen planus (6 months)
49 (M 31)	Lichen planus (3 months)	93 (F 30)	Lichen planus (2 months)
50 (M 28)	Erythema multiforme bul (6 weeks)	94 (F 23)	Neurotic excoriations (2 years)
51 (F 41)	Nail polish dermatitis (3 months)	95 (F 35)	Eczematoid dermatitis (6 months)
52 (F 39)	Soap dermatitis (3 weeks)	96 (F 46)	Eczematoid dermatitis (3 months)
53 (F 36)	Erythema multiforme (6 weeks)	97 (M 28)	Eczematoid dermatitis (1 month)
54 (F 28)	Lichen planus (4 months)	98 (M 38)	Eczematoid dermatitis (8 months)
55 (F 44)	Erythema multiforme (1 year)	99 (F 42)	Onychomycosis (2 years)
56 (M 45)	Pityriasis rosea (1 week)		

*No sensitization or irritation was observed in any of these cases.

Note—The intervening cases (6, 7, 12, 13, 17, 19-23, 25, and 26) were patients whose major diagnosis was bronchial asthma. These patients were also patch tested and the results were negative in all cases.

TABLE 4

EFFECT OF POLYSORB ON HEALING TIME OF EXPERIMENTAL WOUNDS

BASE	MEAN WOUND AREA *(square millimeters)*	MEAN HEALING TIME *(days)*	SHORTEST HEALING TIME *(days)*	LONGEST HEALING TIME *(days)*
Polysorb (anhydrous)	64	13.0	10	16
Polysorb (half saturation)	58	12.6	9	14
Polysorb (three-fourths saturation)	74	13.2	10	16
Polysorb (saturated)	62	12.6	9	15
CONTROL	72	13.3	8	16

Wound healing study—In addition to sensitizing and irritating properties of an ointment base, it is important to determine the possible effects on the healing process of skin. The effect of the base on the healing process of experimental wounds was studied in the general manner described by Dodd, Hartmann and Ward.[5] After shaving the hair from the back of the test animal (rabbit) a series of four excisions was made on each side and the cross-sectional area carefully measured. Three of the experimental wounds on each rabbit were used as controls and five were treated with Polysorb and its hydrated form, at one-half, three-fourths and complete saturation levels. The area of the test wound was measured daily and the formation of new epithelium was defined as a healed area. When the new epithelium over the lesion became continuous, the wound was considered as healed. The base was applied directly to the wound each day and covered with gauze over which was placed a cloth bandage. Wounds that became infected during the course of the experiment were excluded from the study. Since other factors, such as position of the wound and blood supply to the area, markedly influence the rate of wound repair, the mean values are reported in Table 4. Fourteen rabbits with 42 control wounds and 80 treated wounds were used for this study.

DISCUSSION

The clinical safety of a wide variety of dermatologic vehicles has been reported in the literature. Frequently these studies consist of merely a routine patch testing of the active ingredients, on a rather select, limited series of subjects. It should be borne in mind that the dermatologist rarely prescribes medication to be used on normal skin and that a clinical study should include an investigation of the medicament on pathologic skin. It might be expected that pathologic skin will react in a different manner than normal skin. Perhaps the failure of various dermatologic preparations is due to conclusions arrived at from studies carried out on normal skin alone.

It is important to conduct a preliminary screening of the material on laboratory animals. Rabbit skin has been shown to be more sensitive to irritants than human skin. The value of such testing lies in the detection of potential irritants and a more careful study of an agent is indicated when a positive rabbit patch test is obtained. The technic described may be used to rapidly screen a wide variety of mixtures and has the further advantage of reducing the variations from animal to animal to a minimum.

The determination of the clinical safety of any dermatologic vehicle should include the following:

1. Patch testing of rabbit skin with both the base and drug-base mixtures.
2. Patch testing of normal human skin.
3. Patch testing of patients with known allergies.
4. Patch testing of patients with a wide range of dermatoses.
5. Study of the effects of the preparation on the healing process of skin.

In these tests both the base and the drug-base mixtures should be used. The behavior of the commonly used dermatologic agents, in combination with the base, would then serve as a measure for its use in dermatologic practice.

Polysorb is a completely safe dermatologic vehicle as demonstrated by the above protocol. This is in contrast to the reported sensitization and irritation of other bases. Both Polysorb and Polysorb-drug mixtures caused no irritation or sensitization in any of the tests. Polysorb may be used freely by the patient having a known allergy, since it is not sensitizing.

CONCLUSIONS

1. Polysorb is a completely safe dermatologic vehicle that may be used freely in all dermatoses requiring ointment therapy.
2. Polysorb does not interfere with the process of skin repair as evidenced from the study of experimental wounds.
3. Polysorb did not cause or enhance skin irritation or sensitivity when used in combination with the commonly prescribed dermatologic agents.
4. The desirable pharmaceutical properties such as compatibility with drugs, hydrophilic character, spreading qualities and firm consistency complement its superior clinical safety and make it the preferred ointment vehicle.

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Pediatrics

IN GENERAL PRACTICE

For general practitioners, in whose practice is included a major proportion of the medical management of infants and children, and for the specializing pediatrician as well, POSTGRADUATE MEDICINE *presents this special regular department devoted to brief discussions by recognized authorities on their preferred methods of the treatment and management of diseases and problems of infancy and childhood.*

Treatment of Acute Laryngotracheobronchitis

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PRIEST

THIS paper will deal with the treatment of acute laryngotracheobronchitis with respiratory obstruction. A vast number of children and adults have "croupy" respiratory infections which properly can be called "acute laryngotracheobronchitis." Most recover when treated as common colds. Only a few develop the alarming respiratory obstruction which is usually referred to as "acute laryngotracheobronchitis."

Medical treatment includes rest, high humidity, antibiotic and chemotherapy. Most of these need not be elaborated here. Proper humidifiers will be commented upon later.

Some laryngotracheobronchitis patients develop signs of respiratory obstruction before receiving medical treatment. Others become obstructed despite medical management. The rate at which obstruction comes into being varies greatly. It is possible for a child to be dead of laryngeal obstruction two hours after his first symptoms.

Obstruction in acute laryngotracheobronchitis can occur at the upper or lower end of the larynx. Acute inflammatory obstruction of the trachea by swollen mucosa is said to occur but the author has never seen such a case. Tracheotomy relieves the usual acute inflammatory respiratory obstruction because it provides ingress for air *below* the point of obstruction.

Obstruction at the upper end of the larynx is called supraglottic edema or acute epiglottitis or acute hypopharyngitis. It is supposed to be caused mainly by the influenza bacillus but this organism cannot always be recovered. Streptomycin must be considered for use here because of its effectiveness against the *Bacillus influenzae,* but its toxic effects on the eighth cranial nerve must not allow its promiscuous use.

In supraglottic edema a rim of swollen tissue forms around the entrance to the larynx. The epiglottis, aryepiglottic folds and false vocal cords enlarge to narrow the airway. The true cords and subglottic region may be almost uninflamed.

The breathing in these cases is slightly different than in subglottic edema. There is the same picture

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FIGURE 1*a (top)*. Swelling of aryepiglottic folds and arytenoids sometimes present in addition to swelling of epiglottis. *(b, bottom)*. Great swelling of false cords seen in a few cases. Note very small airway remaining.

From: MILLER, ALDEN H.: Acute epiglottitis. Tr. Am. Acad. Ophth. May-June, 1949, pages 519-526.

of air hunger with the anxious face, circumoral pallor and restlessness. But the air seems to go into the lungs easier than it comes out, and the patient talks and acts as if his throat were full. He sounds a little like the peritonsillar abscess patient but has much more marked obstructive signs in his chest. These will be described later when subglottic edema is considered.

When the tongue is depressed the epiglottis in small children can usually be seen easily. In supraglottic edema it is fiery-red, swollen and may even be cyanotic suggesting the appearance of a varix. The epiglottis may be so tense that it will split when picked up with a direct laryngoscope. Direct laryngoscopy ought to be carried out only when one is prepared to go ahead and relieve the obstruction as the examination procedure may precipitate further obstruction.

Subglottic edema occurs more often than supraglottic edema. Patients having subglottic edema have a hoarse voice, a "tight" cough and the same signs of air hunger as the supraglottic edema group (restlessness, circumoral pallor and irritability).

The chest signs of laryngeal obstruction are easy to understand if one considers why they occur. On inspiration the chest capacity is increased mechanically by muscles, ribs and diaphragm. The pressure inside the pulmonary airways is decreased. Atmospheric pressure around the patient pushes air through the larynx into the lungs to equalize the lowered pressure. When the laryngeal airway is not open the atmosphere surrounding the patient tries to get into the chest by pushing in through every soft area of the chest. The suprasternal, supraclavicular, epigastric and intercostal spaces all sink in during inspiration. When the child becomes excited his larynx is narrowed by muscle spasm, his color becomes worse and his anxiety increases. Sticky secretion passing through his larynx produces additional obstruction increasing his anxiety. He tries harder to breathe and there is increased retraction of all the soft areas of his chest.

When confronted by a patient exhibiting these signs, what should one do? One must balance the patient's chances for survival with surgical intervention against his chances without it. Two main factors are to be considered: (1) The degree of airway obstruction. Can the patient get even a minimum oxygen volume through his narrow airway? (2) Is the patient's circulatory system able to stand the overload?

Good surgical judgment is necessary to decide whether tracheotomy needs to be done. In croup, the decision is difficult. In the cases seen early in one's experience, one is likely to be hasty about doing tracheotomy. The parents want the child treated in the safest manner, and one sometimes is hard put to know whether to operate or not.

If a child's color is reasonably good, although signs of narrowing of the laryngeal airway are present, the most important single index of danger is an increasing pulse rate. The pulse should be recorded frequently (every 10 to 30 minutes). If the rate consistently rises, an impending circulatory failure is presaged, and tracheotomy should not be delayed.

If judgment indicates need for intervention to improve the patient's airway, one must choose between emergency and orderly tracheotomy. Both procedures will be described.

EMERGENCY TRACHEOTOMY

This procedure has been described so well by Dr. Chevalier Jackson that his description is quoted here:

Step 1. Throwing the trachea into prominence and fixing it in the midline are accomplished by pushing

back the great vessels well under the sternomastoid muscles. This is done in a second or two with the thumb and index finger of the left hand.

Step 2. Initial Incision—With one sweep of the scalpel an incision is made from Adam's apple almost to the suprasternal notch. This incision must go clear through the skin to facilitate free finger dissection. There may be considerable flow of blood but nothing immediately dangerous.

Step 3. Finger Dissection to Find the Trachea—While the left thumb and middle finger are still holding back the great vessels under the sternomastoids the previously idle left index finger quickly locates the trachea by following downward from Adam's apple. The trachea is infallibly identified by the rigid character of its walls; there is nothing like it in that region. Every medical student has learned, or should have learned, the feel of it in the dissecting room. In identifying the trachea the finger at the same time bares its midline of tissue below the cricoid, by pushing the finger down under any overlying tissue; if the isthmus of the thyroid gland intervenes it is pushed downward and elevated. If it is torn or cut it will not matter. If an anomalous artery is felt crossing the trachea at this point it is pushed downward.

Step 4. Tracheal Incision—The trachea having been identified and bared of tissue, the tip of the index finger is slid slightly to the operator's left side so that the scalpel in the right hand can be safely guided down along the palmar surface of the index finger onto the tracheal wall. Two or three rings are incised. In making the incision the middle finger of the right hand makes a guard against deep entrance of the knife that might otherwise go through the posterior tracheal wall into the esophagus.

Step 5. Holding Apart the Lips of the Tracheal Incision—There is usually a hiss if the patient is breathing, but the lips of the tracheal incision in most cases lie so closely in contact that insufficient air is permitted to pass. The lips should be spread apart with a Trousseau dilator; if none is available a hemostat will do. Lacking these, the handle of the scalpel may be inserted in the slit and rotated slightly to cause gaping. Of course some blood will trickle into the treachea but cough will quickly expel it and spray it about. The cannula is inserted with its pilot; the pilot is removed if not blown out by the tussive blast. If by reason of deplorable lack of equipment no cannula is available someone must hold the lip of the tracheal incision apart until a cannula can be obtained or a makeshift devised for temporary use.

Step 6. Artificial respiration must be done if there has been respiratory arrest. Oxygen mixed with 7 per cent carbon dioxide should be liberated at the tracheal opening or gently insufflated through a catheter. The best cardiac stimulant is to get oxygen into the heart muscle by way of the circulating blood. No drug is a substitute for this.

Step 7. Hemostasis—As soon as respiration is established hemostasis may be done in the usual way. If artificial respiration is necessary, temporary hemostasis may be afforded by packing gauze firmly into the wound and around the cannula.

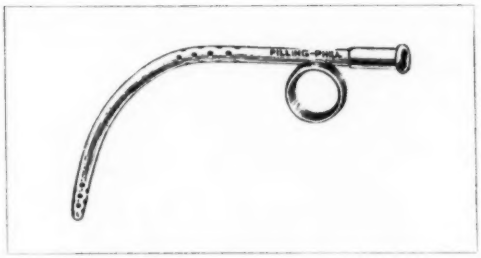


FIGURE 2. Mosher's tube for temporary intubation commonly known as a "lifesaving tube."

From: Boies, L. R.: "Fundamentals of Otolaryngology," W. B. Saunders Company, 1949.

ORDERLY OR TRANQUIL TRACHEOTOMY

Conditions for orderly tracheotomy can be created by inserting a bronchoscope, Mosher lifesaving tube, or endotracheal anesthesia tube through the stenotic larynx to provide a temporary airway. This airway is maintained by an assistant during the time tracheotomy is being carried out.

Technic—In the hands of the occasional surgeon the rule should be that anesthesia ought always to be local unless intratracheal anesthesia is available. Then general anesthesia may be properly considered.

At the University of Minnesota, our usual anesthetic is 1 per cent procaine with epinephrine infiltrated in the midline from the suprasternal notch to the thyroid notch. A rhomboid of injected anesthesia can be made to surround the field with no solution being injected in the midline. We have not used this method.

A midline incision is made from the thyroid notch above to the suprasternal notch below. The knife is carried through the skin and superficial fascia. Bleeding vessels are clamped. Tying may be deferred until just prior to opening the trachea. Often cocaine is injected into the tracheal lumen just before the tracheal wall is incised. The few moments necessary to allow it to produce anesthesia may be used to tie any skin bleeders still in need of ligature.

The midline incision is carried through the deep fascia. If the thyroid isthmus is broad and lies over the trachea where the tube is to be inserted, the isthmus should be divided and then retracted to the sides. Division is carried out by dissecting the thyroid isthmus off the front of the trachea, clamping it and cutting between clamps. A running suture of fine plain catgut or silk is placed in each cut edge of the thyroid to control bleeding before the clamps are removed. Any large veins which interfere with proper placement of the tube are ligated and divided.

Some authors (Waldapfel) advocate a transverse

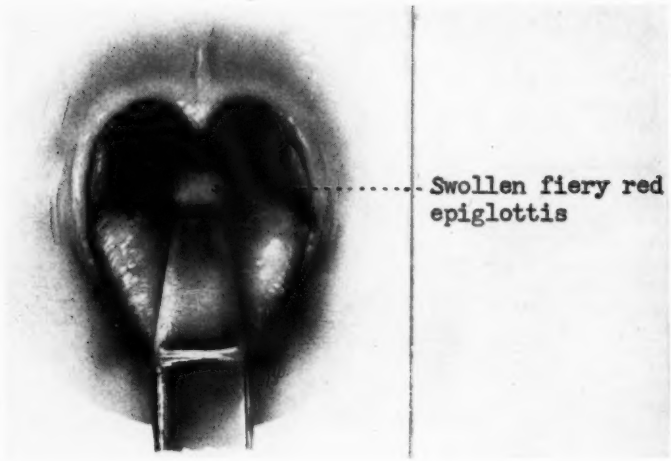


FIGURE 3. Greatly swollen, fiery red epiglottis with *H. influenzae* type B, inflammation easily seen by simple tongue depression.

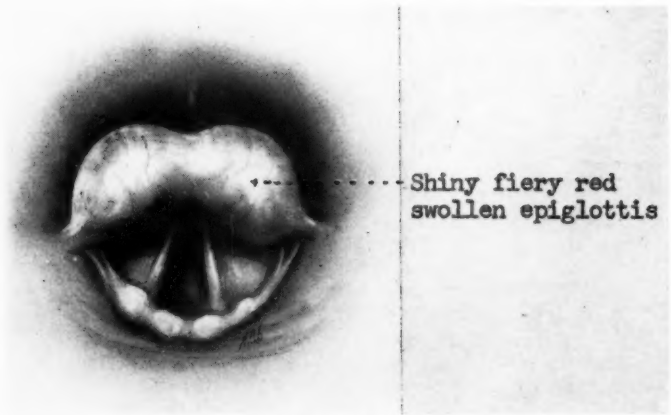


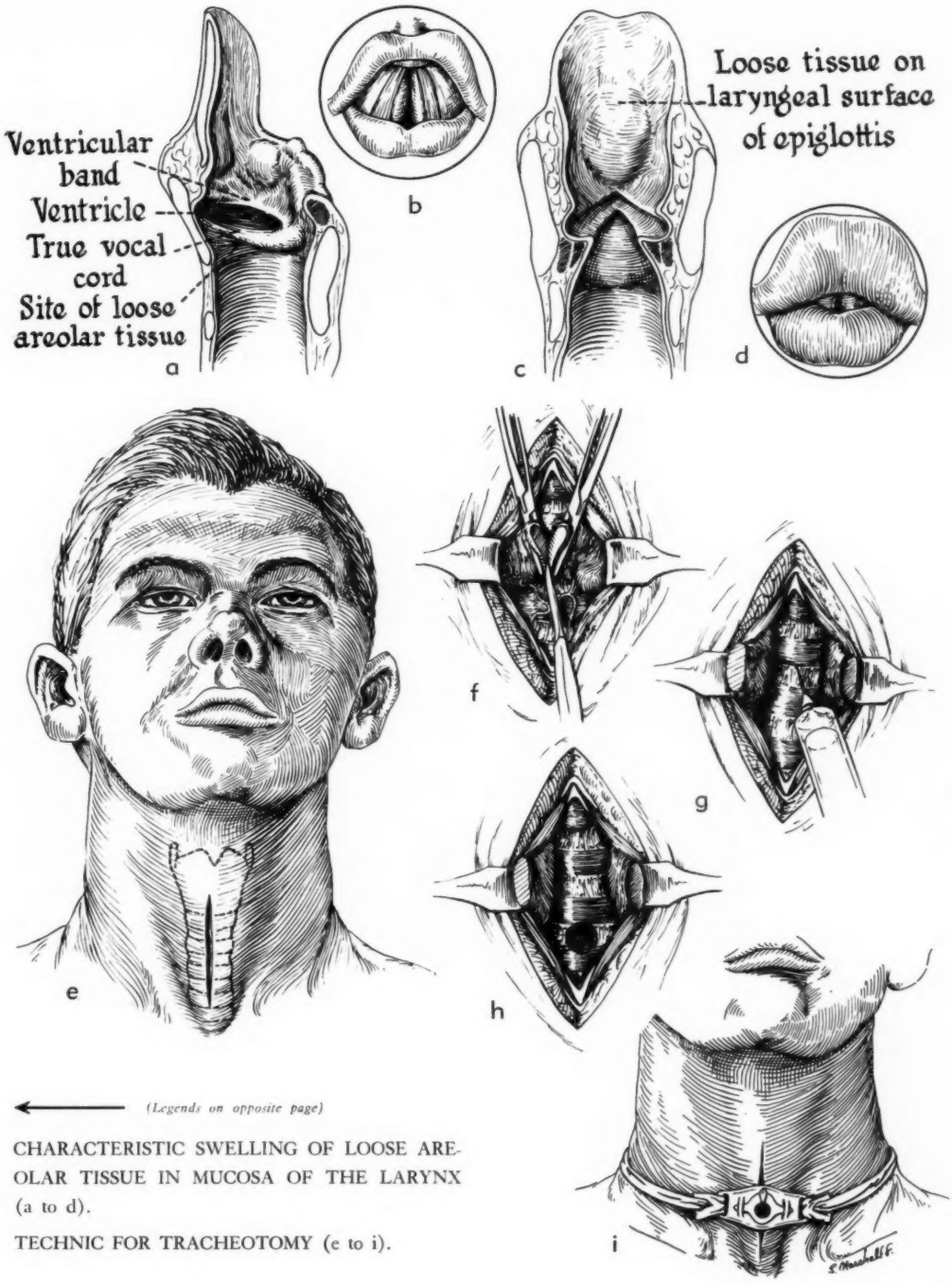
FIGURE 4. *H. influenzae,* type B, epiglottitis as seen by indirect mirror or by direct laryngoscopy examination.

From: MILLER, ALDEN H.: Acute epiglottitis. Tr. Am. Acad. Ophth., May-June, 1949, pages 519-526.

FIGURE 5. There are two sites in the mucosa of the larynx at which there is loose areolar tissue that is prone to swell easily when inflamed. One is subglottic just below the vocal cords (a). The swelling is characteristic at this site in acute laryngotracheobronchitis (b) or after prolonged instrumentation as in bronchoscopy with a relatively tight fitting bronchoscope. The other site is on the laryngeal surface of the epiglottis (c), which swells rapidly when acutely inflamed as part of the picture of supraglottic inflammation (d).

Important in the technic for orderly tracheotomy are (e) an adequate incision; (f) careful hemostasis when the isthmus of the thyroid has to be divided, (g) injection of a few drops of 5 per cent cocaine into the trachea a few minutes before the trachea is opened, (h) removal of a disk of tissue below the second tracheal ring in an average case. This disk should be just slightly larger than the diameter of the lumen of the tube to be used so that it will slip in and out easily, and (i) avoidance of sutures in the tracheotomy wound except possibly at the ends. Air is invariably coughed out around the tube within the few hours after tracheotomy and if the wound is closed snugly, emphysema of the soft tissues invariably develops and more or less reaction in the wound.

From: BOIES, L. R.: "Fundamentals of Otolaryngology," W. B. Saunders Company, 1949.



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CHARACTERISTIC SWELLING OF LOOSE AREOLAR TISSUE IN MUCOSA OF THE LARYNX (a to d).

TECHNIC FOR TRACHEOTOMY (e to i).

incision of the fascia above the thyroid isthmus to free the isthmus, which may then be retracted downward and the tube properly placed without incision of the isthmus. No harm is done by division of the thyroid isthmus and the essential object is proper placement of the tracheotomy tube. At the University of Minnesota, we have practiced division of the thyroid isthmus whenever necessary.

After division of the thyroid isthmus, the tracheal rings can be seen through the thin fascia overlying them. The operator should reorient himself at this time. He should palpate the cricoid cartilage in the midline anteriorly and should count down to the third tracheal ring. *If there is any doubt in the operator's mind as to exactly where he should incise the trachea, he should take time to find out before he opens the trachea.* There is no more miserable or difficult problem than that of difficult decannulation, and this problem can only be avoided if the incision in the trachea is properly placed.

One or two cubic centimeters of 2 to 4 per cent cocaine solution are injected into the lumen of the trachea a few minutes before the incision into the tracheal wall is made. This makes the actual opening of the trachea quite a tranquil procedure, with little coughing and struggling on the part of the patient.

It has been our practice at the University of Minnesota to perform the punch operation of Mosher. A midline incision is made through the second, third or fourth rings, depending upon the accessibility of the trachea. An Allis forceps is then used to seize the tracheal cartilage through the incision, and a semilunar piece is removed from the anterior tracheal wall on the right and left sides of the incision. Mosher originally used a ring punch to remove the button of cartilage. Removal of a circular piece of the anterior tracheal wall permits easy insertion of tracheal cannulas and prevents deformity of the tracheal cartilages by pressure from the cannula. The circular "button" of cartilage thus removed is about the size of the tracheotomy tube to be inserted. Another type of punch has been described by Waldapfel for removing this tissue, but we have had no experience with it. Before the trachea is opened a soft rubber urethral catheter is attached to the suction apparatus. This catheter is inserted into the trachea to aspirate blood or secretions.

The tracheotomy wound is not closed, and the only dressing applied is the gauze squares cut or perforated and placed around the tracheotomy tube. A tube is selected according to the patient's age and is inserted to a distance just proper to allow free breathing without danger of being dislodged. Care is taken not to allow a long tube to impinge on the anterior tracheal wall and thus produce cough, granulations or bleeding.

We have used the Jackson tubes made by Pilling exclusively because of their availability, proper curvature and generally satisfactory design.

The tape around the patient's neck is tied in a square knot (not a bow knot) and is preferably tied on one side rather than behind where the knot causes discomfort to the patient as he lies on his back.

ERRORS AND ACCIDENTS ACCOMPANYING TRACHEOTOMY

1. Too short an incision prolongs the operation and makes it more difficult. The incision is inconspicuous after it heals in most cases. Cosmetic surgery and safe surgery are not always compatible. The longer incision certainly makes tracheotomy safer by bringing all parts of the operative field into clear view.

2. After incision of skin and superficial fascia the next layer may not be separated in the midline and the operator may become disoriented.

3. The dome of the pleura may be punctured as it bulges up into the wound, and pneumothorax may be induced.

4. The knife used to incise the trachea may be carried through the posterior wall of the trachea into the esophagus.

5. The cannula may fail to enter the tracheal lumen and may make a false passage outside the trachea. This is not as apt to occur if a "button" of the tracheal wall has been removed as described in the section on operative technic (Mosher's punch operation).

6. The operator may fail to identify the cricoid cartilage before he opens the trachea. This may lead to division of the cricoid and subsequently to laryngeal stenosis.

7. An improperly fitted tube causes erosion of structures pressed upon and may lead to various undesirable complications.

8. Entrance of blood into the trachea can be prevented by proper hemostasis unless there is urgent need for opening the trachea. If dyspnea is marked a small amount of bleeding can be ignored and the patient turned after insertion of the cannula so that the blood will not run into the trachea. The bleeding can be controlled later if it does not stop spontaneously.

POSTOPERATIVE COMPLICATIONS

1. Emphysema of subcutaneous and fascial layers of neck occurs when air is forced into the tissues through the tracheotomy wound. Suturing of the wound favors the production of emphysema. Packing of the wound with vaseline gauze decreases the ease with which air is forced into the tissues. Some surgeons impregnate this gauze with sulfonamide drugs.

Emphysema of the mediastinum has occurred in several of our cases at Minnesota but no serious result has ensued. Pneumothorax may follow emphysema of the mediastinum or may be produced by puncturing the dome of the pleura as it projects up into the neck wound. This complication is serious and must be dealt with by physicians accustomed to handling pneumothorax. Unless the pneumothorax is bilateral it usually is not a fatal complication.

2. Blood in the mediastinum was found at autopsy in one case but it was not definitely established that this was not a postmortem artifact.

3. Laryngeal or tracheal stenosis need not follow properly done tracheotomy.

4. Wound infections are rare particularly since antibiotic therapy and chemotherapy have been available.

5. Tracheitis usually follows tracheotomy. This is transitory. Excessive tracheal secretion is produced for a few days but after a week or ten days this decreases markedly.

POSTOPERATIVE CARE

Dr. Chevalier Jackson has emphasized in his writings that tracheotomy is not an object in itself. It is done to permit the patient to get air into his lungs. All the aftercare is directed at keeping the tracheotomy tube open and the wound clean.

When the patient goes to his room from the operating room, an exact duplicate of his tracheotomy tube is sent with him. It is most important that this tube be supplied with its own inner tube and obturator. Obturators and inner tubes usually fit only their own outer cannula. Lack of a proper obturator may be a very serious matter, if it delays changing of a tracheotomy tube. The extra tube is kept sterile on a tray with supplies for instant changing of the tracheotomy tube in case of any emergency.

In addition to the tray containing the extra tube and its supplies, a general utility tray is provided. This holds the solution and materials for cleaning the inner cannula, as well as the suction tubing. The use of this tray will be discussed.

Upon his return from the operating room, the patient is placed in a bed with the head elevated. The pillow is rubber covered. Water or portable machine suction is in the room at all times. The suction is so placed as to be instantly available for use in tracheal aspiration. The rubber catheter is always connected to the suction tube.

When the air of the patient's room is dry, it must be moistened to aid in the liquefaction of tracheal and bronchial secretions. Various methods of humidification have been used. These include:

1. The patient's bedroom is rendered moist by cold humidifiers which spray a fine mist into the air by a centrifugal action.

2. A nebulizer may be connected to the tracheotomy tube and forcing of air or oxygen through the nebulizer from a tank of compressed gas, as described by Albers.

3. A centrifugal cold humidifier may be connected to an oxygen tent as advocated by Davison.

4. An atomizer spraying into an oxygen tent as described by Platou.

5. A moistened gauze sponge may be placed over the tracheotomy tube and may be replaced frequently.

6. Instillation of normal saline into the tracheotomy tube with a dropper. Proper precautions to prevent breakage of the dropper and entrance of glass into the trachea must be taken. The use of a short piece of rubber catheter on the end of the dropper minimizes the danger of glass fragments entering the trachea.

The patient is closely watched for hemorrhage and for closure of his tube by secretions or blood. The inner tube is suctioned frequently. When the rubber catheter is introduced into the tracheal cannula, the catheter is pinched shut until it has been inserted as far as necessary. This prevents the tip of the catheter from engaging the tracheal wall, or other tissue during introduction. Some surgeons instill normal saline into the trachea before tracheal aspiration is done. The saline loosens crusts and dilutes thick secretions. Some surgeons limit the extent to which the catheter can be inserted by the nurse by wrapping a collar of adhesive tape around the catheter.

The inner cannula is changed every two to four hours, as ordered by the surgeon. It should not be left out of place for more than ten minutes at the longest. The outer tube is thoroughly sucked out before the inner tube is replaced. If this is not done, accumulated secretion is pushed into the trachea by the inner tube as it is introduced. The inner tube is cleaned by pushing a pipe cleaner through it. To clean an inner tube properly with an ordinary applicator is impossible.

The outer tube and the dressings are usually changed daily by the doctor, but some physicians change the outer tube at longer intervals.

DECANNULATION

This is accomplished in patients having properly performed tracheotomies by simple removal of the cannula after the patient has demonstrated his ability to breathe with the cannula closed for 24 to 48 hours. We have used rubber plugs whittled out of large rubber corks to close our cannulas. It is important to use rubber stoppers, as fragments of ordinary cork may become pulmonary foreign bodies. These rubber stoppers should be secured to the tape encircling the patient's neck by a piece of thread 6 to 8 inches long. They are tethered by this

thread when blown out of the tracheal tube if the patient coughs. In some cases half-round corks are used to partially occlude the lumen before full corking is done. Some surgeons use the obturator of the tracheotomy cannula as the stopper when trying out the patient's ability to get along with his tube occluded. We have not felt that this was quite as safe as the method outlined previously.

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Treatment of Meningitis

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The treatment of meningitis has undergone rapid changes in the past few years. In a comparatively brief time the treatment has changed from serum to antitoxin, to sulfonamides, to penicillin, to aureomycin, and to streptomycin. The treatment of meningitis reflects the rapid strides medicine has made in the past decade, and may serve as an index of medical progress.

LEVINSON

We shall first discuss the general treatment of meningitis and later elaborate on the treatment of specific types of the disease.

The most important remedies for meningitis are sulfonamides, penicillin, aureomycin, and streptomycin. Other antibiotics, such as chloromycetin, have been used, but their value is still limited. In addition to the above, promizole and para-aminosalicylic acid have been used as adjuvants to streptomycin. Rabbit influenza-meningitis serum has been advocated for influenzal meningitis.

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SULFONAMIDES

Sulfadiazine is the sulfonamide of choice in the treatment of meningitis, although good results have also been obtained with other sulfonamides. The sulfonamides can be given either intravenously, orally, or subcutaneously. In most cases of meningitis we want to get as fast action as possible; it is, therefore, best to give the sulfonamides intravenously. We give half of the daily dose initially and then repeat it in four to six hours, depending on the patient's condition. For intravenous injection we use 5 per cent solutions of sodium sulfadiazine, dissolved in distilled water, saline, or Hartmann's solution given by the drip method. Sulfonamides are no longer given intrathecally although in the early days this method was used extensively. We follow the rule of leaving the needle in after the intravenous injection of the sulfonamide, giving additional fluid with a maintenance requirement of 100 cc. per kilogram of body weight.

The dosage varies with the age of the patient and the virulence of the disease. We have adopted a standing rule of giving 3 gr. per pound of body weight in 24 hours, in divided doses, but never more than 5 gm. as the initial dose. This holds true for both children and adults. As soon as the patient can take sulfonamides by mouth, it may be given

orally, in the same dose, 3 gr. per pound of body weight in 24 hours. The initial dose for oral administration is half of the total 24-hour dose or 1½ gr. per pound of body weight. Sulfonamides may also be given subcutaneously in 1 or 2 per cent solution. Here too the dosage should be 3 gr. per pound of body weight in 24 hours.

One should keep in mind the fact that sulfonamides may produce some untoward manifestations. The complications that may follow are: nausea, vomiting, diarrhea, jaundice, rashes, mental depression, ringing of the ears, neuritis, agranulocytosis, and hematuria. The sulfonamides should be discontinued when agranulocytosis or hematuria appears.

PENICILLIN

Penicillin is effective in several types of meningitis. We have been giving 50,000 units every three hours, intramuscularly, in pneumococcic meningitis and 400,000 units of penicillin once a day in other types of meningitis. Penicillin does not produce as many toxic effects as the sulfonamides but occasionally it does result in a cold abscess. The abscess often disappears on the administration of antihistamines. We have seen 2 cases of toxic encephalitis due to penicillin. We no longer give penicillin intrathecally. However, should one choose to give it intrathecally, as some of the eastern physicians do, it should be dissolved in a very small amount of water, and injected very slowly, as large amounts may increase the intracranial pressure, which is already very high in meningitis.

STREPTOMYCIN

Streptomycin has been found useful in influenzal and in tuberculous meningitis. We give it only intramuscularly, although some clinicians still administer it intrathecally.

Streptomycin may cause deafness. Occasionally there is also a paresthesia of the hands and tongue. Some of our streptomycin-treated cases had a subarachnoid block with xanthochromia. It is, however, difficult to decide whether that condition was due to the streptomycin or to the disease itself. The question arises whether less frequent doses would produce fewer complications, particularly deafness. Our impression is that the frequency of the administration has no effect on the complications. The question has also been raised whether the length of time streptomycin is given has any effect on the deafness. Only future clinical experience will settle that. If it is true, as we think it is, that more frequent doses and more prolonged streptomycin administration serve to prolong the patient's life, the gain compensates for the loss of hearing.

AUREOMYCIN

Aureomycin has been found effective in pneumococcic, meningococcic, and influenzal meningitis, but it is most useful in influenzal meningitis. Aureomycin may be given both intravenously and intramuscularly. Vomiting occurs not infrequently after its administration. This may be prevented by giving it in applesauce or alkaline water. Thrombophlebitis occurs occasionally after intravenous administration.

CHLOROMYCETIN

Chloromycetin is useful in typhoid meningitis and may be of value in colon and salmonella meningitis.

CONCENTRATION

The concentration of antibiotics and chemotherapeutic agents in the blood and in the cerebrospinal fluid has been used as a criterion of treatment, but it is not the only criterion. We have seen children who recovered in spite of a poor concentration and vice versa. The concentration that we found most effective in meningitis was 13 to 15 mg. per 100 cc. of blood, although 5 mg. per 100 cc. of blood suffices in most infections. As a rule when the therapeutic agent is given intravenously, a high blood level is reached immediately or in 15 minutes. The cerebrospinal fluid concentration varies. In some cases it reaches about 80 per cent of the blood concentration and in others only 30 per cent.

SENSITIVITY

Of greater importance than the concentration of the therapeutic agent in the blood and cerebrospinal fluid is the sensitivity of the organism to the respective antibiotic or chemotherapeutic agent. Sensitivity tests should therefore be done in all of the cases.

RESISTANCE

In some cases the organism becomes resistant to the antibiotic or chemotherapeutic agent. This is particularly true in the case of streptomycin. Resistance tests should be done when the patient does not respond to treatment.

PROMIZOLE

Promizole has been advocated as an adjuvant to streptomycin in tuberculous meningitis.

PARA-AMINOSALICYLIC ACID

This drug has also been advocated as a good adjuvant to streptomycin in tuberculous meningitis. This claim has not yet been substantiated.

SERUM AND ANTITOXIN

Before the chemotherapeutic and antibiotic era, serum had its place in the treatment of meningitis. Now that the mortality has dropped to 10 per cent or less with antibiotics and chemotherapy, serum no longer has a place in the treatment of most meningitides. Alexander antirabbit serum may, however, be used when a patient with influenzal meningitis does not respond to streptomycin or aureomycin. When used it should be given in large doses. We give 100 mg. intravenously, and repeat in 24 hours.

In treating meningitis we must remember that while the specific effect can be obtained by antibiotics and chemotherapy, the patient's nutrition must not be neglected. If a patient is dehydrated he should get glucose. In severe cases of dehydration as in tuberculous meningitis, where the patient is emaciated and has a scaphoid abdomen, the patient should also get amino acids. Blood transfusions are also valuable, repeated small transfusions being preferable to one large one. The patient also needs an extra supply of vitamins. We give 200 mg. of vitamin C in the parenteral fluid and vitamin B complex, injectable, in 25 mg. doses. This is empirical but valuable.

Attention should be paid to symptomatic treatment. One of the most important symptoms is convulsions and every means of stopping them should be taken. Cardiorespiratory collapse should be treated by caffeine, adrenalin, and oxygen. Every child with meningitis should be examined periodically for sequelae, which in the main are: encephalitis, hydrocephalus, blindness, deafness, paralysis, and mental deficiency.

TREATMENT OF SPECIAL TYPES OF MENINGITIS

Meningococcic meningitis—Good results are obtained in meningococcic meningitis with sulfonamides alone or with penicillin alone. However, it is advisable to combine sulfonamides with penicillin to make doubly sure.

Pneumococcic meningitis—Penicillin is the standard treatment. Aureomycin is also effective.

Influenzal meningitis—Streptomycin is very effective in the treatment of influenzal meningitis. We usually give 300,000 units of streptomycin every six hours but in severe cases we give 200,000 units every three hours. We give sulfonamides in addition, to combat secondary invaders. We usually do not find it necessary to give the streptomycin for a longer period of time than seven or eight days. However, we continue the sulfonamides for 14 days. Recently Dr. Rowine Brown and I used aureomycin in the treatment of influenzal meningitis with good results. We administer 100 mg. of the injectable aureomycin intravenously twice a day for five to seven days. We also give 100 mg. tablets orally twice a day for seven to eight days.

Tuberculous meningitis—Streptomycin does not always cure tuberculous meningitis, as relapses occur. It does, however, prolong life. Very often the patient improves in a few days, becomes less drowsy, less irritable and the temperature gradually comes down to normal. Streptomycin should, therefore, be given in every case of tuberculous meningitis. There has been no uniformity of opinion about the dosage and the intervals; we administer 200,000 units every three hours and continue it for three months.

Lincoln and Kirmsey combine promizole with streptomycin. They give 1 gm. in 2 divided doses daily the first week and the second week increase it to 2 gm. and keep the patient on promizole for a long period of time. They claim that promizole when added to streptomycin increases the effectiveness of streptomycin.

The main problem in streptomycin-treated cases is recurrence. Some recur in two months, some in three months, and some a year later. We treat all recurrences with streptomycin and promizole.

The last word has not yet been said in the treatment of meningitis, but sufficient advances have already been made to reduce the mortality of the disease considerably.

COMING POSTGRADUATE COURSES

University of Michigan Medical School, Department of Postgraduate Medicine, Ann Arbor
Diseases of the heart, March 19-23
Endocrinology and metabolism, March 26-30
Rheumatic disease, April 2-6
Allergy, April 9-13
Diseases of the blood, April 16-20
Diseases of the gastrointestinal tract, April 23-27
Recent advances in therapeutics, May 3-5
Electrocardiographic diagnosis, August 27-September 1
Neurology, clinical, May 14-17
Obstetrics and gynecology, February 19-March 3
Ophthalmology conference, April 23-25
Pediatrics, February 28-March 3
Roentgenology, diagnostic, April 16-20

University of Kansas School of Medicine, Kansas City
Public health and preventive medicine, February 12-14
Physical medicine and rehabilitation, February 19-21
Internal medicine, including psychiatry and dermatology, March 19-22
Ophthalmology and otolaryngology, April 16-20
Applied neurology, April 30-May 3

University of Minnesota Medical School, Minneapolis
Continuation course in geriatrics, for internists and general physicians, January 4-6. Visiting faculty members include Dr. E. V. Cowdry, St. Louis; Dr. William Dock, Brooklyn; Dr. Nathan Shock, Bethesda; Dr. E. J. Stieglitz, Washington, D. C., and Dr. E. L. Tuohy, Duluth

Scientific Exhibit

Management of Breast Lesions

THOMAS A. SHALLOW,[1] SHERMAN A. EGER[2] AND FREDERICK B. WAGNER, JR.[3]

JEFFERSON MEDICAL COLLEGE AND HOSPITAL, PHILADELPHIA

The purposes of this exhibit are:

- To show that watchful waiting is a very dangerous practice when one is dealing with any tumor of the breast.
- To present a method of biopsy designed for the detection of early and obscure cancer.

These objectives are illustrated by a group of patients in some of whom bad results were encouraged by waiting, while in others good results were encouraged by early intervention. *Nothing is to be gained by waiting except clinical proof of carcinoma.*

The Earliest Sign of Breast Cancer Is the Presence of a Lump, No Matter How Small

When clinical features of malignancy are present, the lesion is no longer early. Therefore, it is always dangerous and often tragic to wait for a lump in the breast to develop any of the following signs: Nipple retraction, eczema, or discharge; dimpling of the skin; cutaneous edema or pitting with threatening ulceration; fixation to chest wall; metastasis.

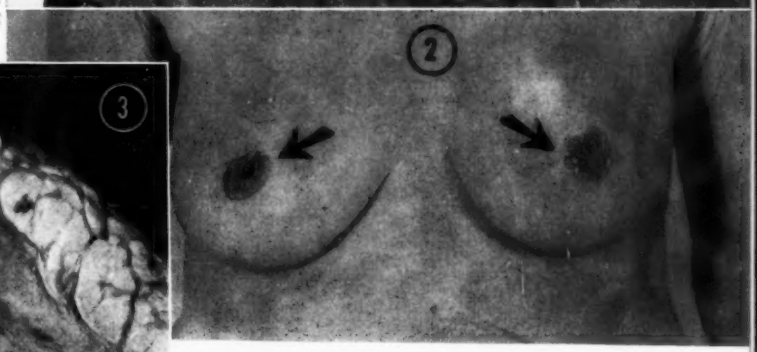

FIGURE 1. Extensive cancer retracting nipple. FIGURE 2. Bilateral Paget's disease, seemingly a surface lesion. FIGURE 3. Paget's disease is actually a penetrating cancer.

Scientific Exhibit shown at the Pennsylvania State Medical Society (99th Session), Pittsburgh, September, 1949.

[1]*Professor of Surgery;* [2]*Associate Professor of Surgery;* [3]*Associate in Surgery.*

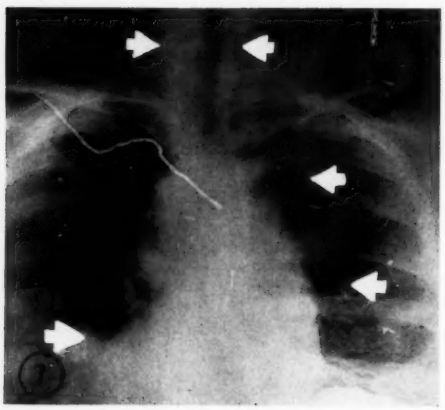

FIGURE 4. Late dimpling of the skin.

FIGURE 5. Cutaneous edema or pitting with threatening ulceration. Orange peel skin.

FIGURE 6. Fixation to chest wall. Upper arrow indicates fixed cancer; lower arrow, benign lesion.

FIGURE 7. Metastasis.

DON'T DEPEND UPON YOUR CLINICAL IMPRESSION IN BREAST TUMORS

Case 1—M. T., married female, age 33. The patient noted a lump one-half inch in diameter in the upper outer quadrant of her right breast, associated with dull intermenstrual pain. Four months later she consulted a physician who referred her to the hospital. Physical examination revealed no definite signs of malignancy and the lesion was thought to be a fibroadenoma.

Biopsy: The entire lump and a wide zone of surrounding breast tissue were removed.

Pathologic report: Frozen section examination revealed scirrhous carcinoma, surrounded by an area of chronic cystic mastitis and a small fibroadenoma.

Treatment: Radical mastectomy was performed immediately. No metastases were found.

Comment: The finding of malignancy was a surprise in this case, but nevertheless the surgeon and operating room were prepared for immediate radical mastectomy.

A BREAST WITH CHRONIC CYSTIC MASTITIS CAN ALSO CONTAIN CANCER

Case 2—M. C., married female with three children, age 32. Two years previously the patient found a lump in the right breast which varied in size with her menstrual periods and seemed to disappear three months later when she became pregnant. One month after delivery she stopped nursing her baby, and shortly thereafter accidentally found a lump in the lower inner quadrant of her right breast which was tender but not painful. It varied in size with menstruation. Since it did not disappear during the ensuing year she consulted her physician who advised prompt hospitalization.

There were no diagnostic signs of malignancy. It was thought to be a case of chronic cystic mastitis.

Biopsy: The lower inner quadrant of the right breast was removed.

Pathologic report: Frozen section examination revealed low grade cancer surrounded by chronic cystic mastitis.

Treatment: Radical mastectomy was performed immediately. No metastases were found.

Comment: It was a distinct surprise to find cancer in this breast, since clinically the features were those of chronic cystic mastitis. This case illustrates the danger in assuming any case to be cystic mastitis on clinical grounds alone and also the great harm that could follow a policy of "watchful waiting."

WHY WAIT FOR CHARACTERISTICS OF CARCINOMA OF THE BREAST TO DEVELOP?

The absence of symptoms, the lack of malignant characteristics, and the youth of the patient are no excuses for delaying investigation. Those cases in which the clinical findings indicate a benign lesion likewise offer no excuse for delay, since it is impossible on clinical grounds alone to rule out malignancy with certainty. Furthermore, those cases which are clinically benign offer the best chance for permanent cure when proved malignant by early biopsy. Clinical signs of cancer are evidenced only by well advanced lesions. Only localized lesions of the breast, regardless of the age or sex of the patient should be subjected to biopsy.

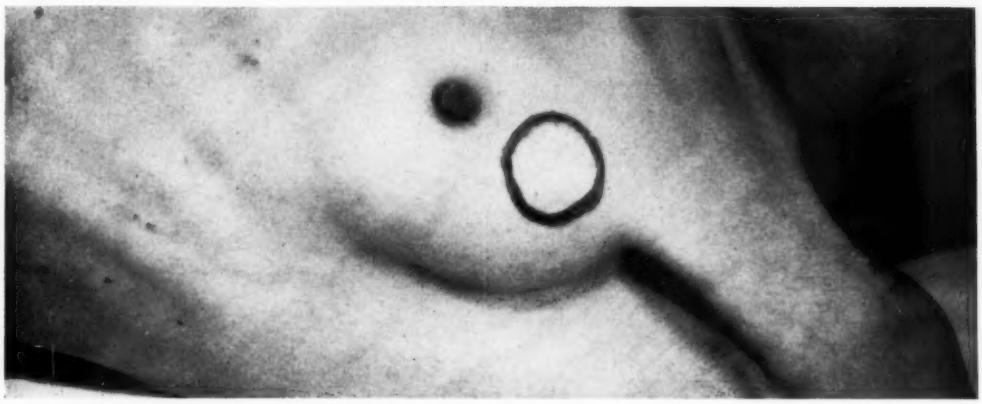

FIGURE 8. Tumor outlined.

HOW TO PERFORM A BREAST BIOPSY: BEFORE OPERATION

Rule out metastasis to lungs and spine by x-ray.

Obtain a signed statement from the patient, for legal purposes, permitting the surgeon to perform whatever operation he chooses.

Outline the tumor, single or multiple, on the overlying skin with indelible ink, to avoid error *(above)*.

The pathologist should be prepared to do an immediate frozen section examination.

The surgeon and operating room should be prepared for radical mastectomy in all cases.

CANCER IN THE YOUNG

Case 3—R. N., married female with one child, age 22. While bathing, the patient accidentally discovered a small lump in the upper outer quadrant of her right breast which had produced no symptoms. Examination by her physician the next day confirmed this, but there were no signs of malignancy. The physician advised prompt hospitalization for removal of the mass, which was done one week later.

Biopsy: Although the palpable lesion was only 1 cm. in diameter, the biopsy was wide and measured 9 x 5 x 4 cm. through a skin incision 7 cm. long.

Pathologic report: Frozen section examination revealed anaplastic medullary carcinoma.

Treatment: Radical mastectomy was performed. No metastases were found.

Comment: A clinically benign breast lesion may be malignant, even in a very young patient.

NIPPLE DISCHARGE MAY BE DUE TO MULTIPLE DUCT LESIONS

Case 4—I. S., single female, age 33. The patient had a straw-colored discharge from the right nipple for three months, with generalized tenderness of both breasts, particularly the right. Her physician promptly sent her to the hospital. No mass was palpable in either breast.

Biopsy: The entire duct system of the right nipple and a generous portion of the upper outer quadrant of the breast, measuring 12 x 10 x 2.5 cm. was removed.

Pathologic report: Frozen section report was duct papilloma—nonmalignant.

Treatment: The breast was reconstructed. During the next few days, while the patient was still in the hospital, serial sections of the biopsy specimen revealed six papillomas, one of which was malignant (duct carcinoma). Radical mastectomy was then performed. No metastases were found.

Comment: When there is a discharge from the nipple, there may be multiple duct lesions. The biopsy specimen should therefore contain the entire duct system. Frozen section is not infallible, and when benign should be followed by careful and unhurried serial examination of the fixed specimen.

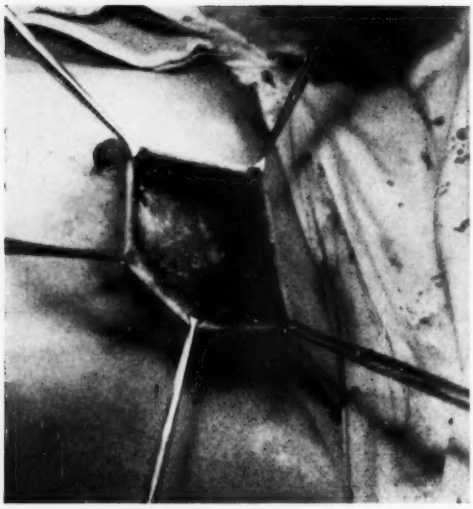

FIGURE 9. Skin undermined.

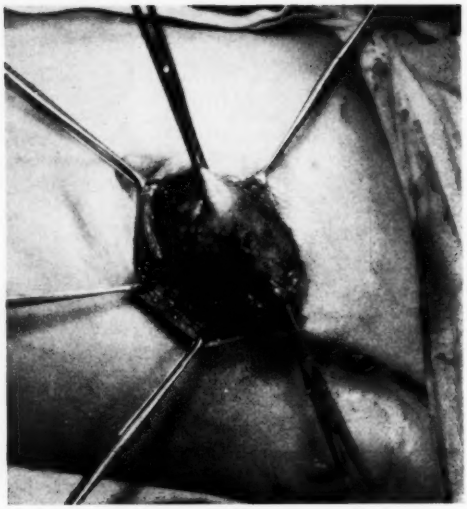

FIGURE 10. Removal of specimen nearly completed.

AT OPERATION

Use a general anesthetic to avoid psychic trauma.

The skin incision should be generous.

The biopsy specimen should include the entire lesion with a wide margin of surrounding tissue down to the pectoral sheath.

This requires removing a fourth or more of the breast in many cases, particularly when the lesions are multiple.

In discharge from the nipple or suspected lesion of the ducts, the entire duct system should be freed from the nipple and removed for examination.

The pathologist should examine the entire specimen for cancer and not merely one portion of it. Only by this method is it possible to diagnose early and clinically undetectable cancer.

A conference between surgeon and pathologist in certain instances, or the insertion of one or more identification sutures in suspicious areas greatly aids the pathologist.

Proper breast reconstruction minimizes deformity.

The patient should remain in the operating room under anesthesia until the report of the frozen section has been received, in order to avoid embarrassment and confusion.

A frozen section report of cancer demands immediate radical mastectomy.

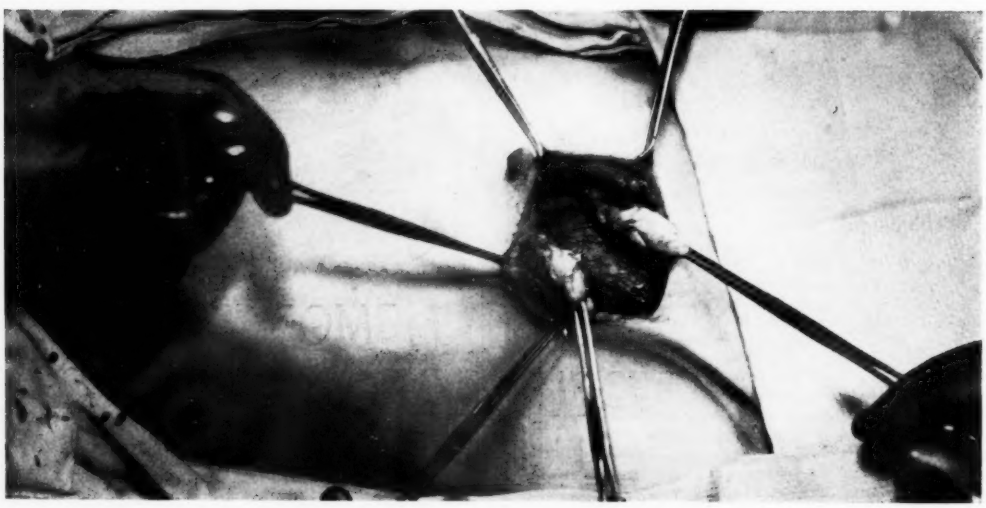

FIGURE 11. Removal complete exposing pectoral muscle.

FIGURE 12. Identification suture.

AFTER OPERATION

When the frozen section report is benign, the patient and family should not be given a final opinion until the fixed specimen has been examined histologically.

WE DO NOT RECOMMEND ASPIRATION BIOPSY OF ANY BREAST LESION, BECAUSE:

Tissue obtained may not be from the cancer area and radical surgery therefore delayed.

The amount of tissue obtained may be insufficient to rule out cancer with certainty, necessitating surgical biopsy anyway.

Ecchymosis and hematoma frequently follow. *(See Case 7.)*

The simplicity of its performance encourages its promiscuous use outside of the operating room, without provision for immediate radical mastectomy.

Breast Biopsy Is Never An Office Procedure

FIGURE 13. Operation completed.

FIGURE 14. Skin graft.

PRACTICAL REMARKS

Cancer

Early cancer may mimic benign breast lesions, also coexist with them or with systemic diseases.

It is not necessarily a fatal disease in young women.

Inflammatory carcinoma, as well as carcinoma during pregnancy or lactation, have the poorest prognosis of all breast lesions. Wide excision and skin grafting versus roentgen therapy is debatable.

Postoperative roentgen therapy is employed in selected cases—when there is lymph node involvement at operation or when painful metastases develop.

Duct Lesions

Duct papilloma is frequently multiple, even though only a single lesion is evident clinically. The obvious lesion producing serous or bloody discharge from the nipple may be benign, but a malignant lesion may be harbored in an adjacent duct. *(See Case 4.)*

Although cancer of the ducts is usually associated with discharge from the nipple, it may occur without discharge.

Chronic Cystic Mastitis

It is safer to regard chronic cystic mastitis as a precancerous lesion.

WATCHFUL WAITING JEOPARDIZES THE PATIENT'S CHANCES OF PERMANENT CURE

Case 5—M. S., married female, age 40. During a general examination her physician discovered a small lump in the upper outer quadrant of the left breast which had produced no symptoms. He advised her to "forget about it." Eleven months later she consulted a second physician who promptly had her admitted to the hospital for biopsy.

Biopsy: Although the palpable lesion was 3 cm. in diameter, the biopsy was wide, and measured 10 x 6 x 3 cm.

Pathologic report: Frozen section report was scirrhous carcinoma surrounded by chronic cystic mastitis.

Treatment: Radical mastectomy was performed immediately. No metastases were found.

Comment: This patient's chances of permanent cure would certainly have been much greater if operation had been performed when the lump was first detected by her physician eleven months previously.

A TRAP FOR THE UNWARY SURGEON

Case 6—M. F., married female, age 35. For four years, the patient noted a painless pea-sized lump in the lower quadrant of her right breast. The lump remained symptomless and did not increase in size. Four years later she consulted her physician following the reading of a magazine article recommending that all lumps in the breast be investigated. There were no signs of malignancy, so the physician removed it without making provision for frozen section examination.

Pathologic report: Routine report three days later was scirrhous carcinoma, surrounded by chronic cystic mastitis.

Treatment: The physician referred the case for radical mastectomy. No metastases were found.

Comment: The lesion was considered benign by her physician to such an extent that frozen section examination was not deemed necessary, let alone radical mastectomy. It must be remembered that a lesion obviously benign clinically can be malignant. One look with the microscope is better than 40 thinks. In this case the physician, patient, and operating room were all unprepared for radical mastectomy.

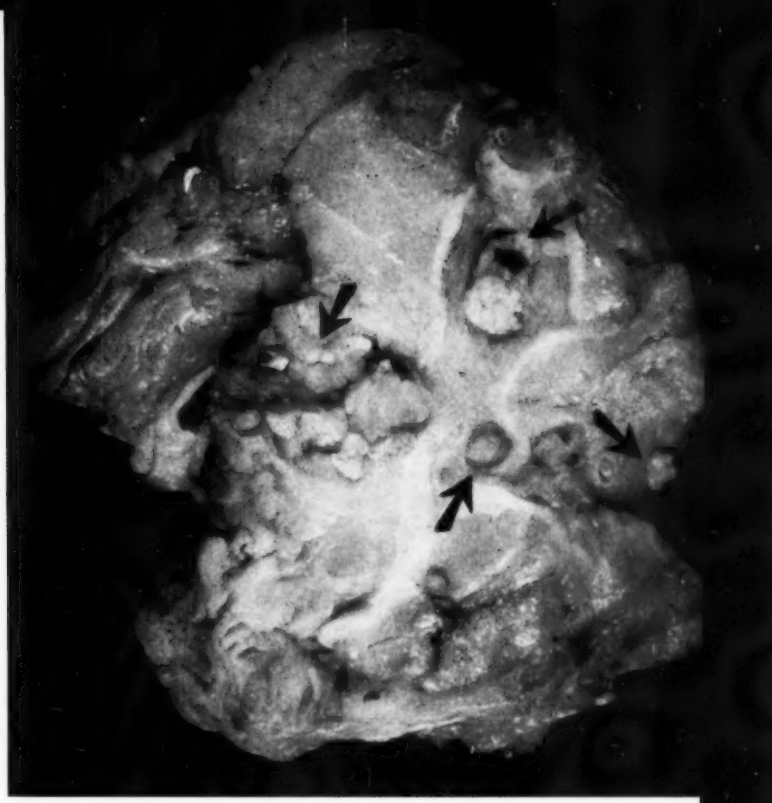

FIGURE 15. Multiple papillomata.

Biopsy should be performed promptly, because:

a. A breast with chronic cystic mastitis can also contain cancer. *(See Case 2.)*

b. The lesion may actually be a cancer. *(See Case 3.)*

Chronic cystic mastitis does not necessarily regress after the menopause.

SUMMARY

Investigate all breast lesions immediately in order to precede malignant evolution in a benign lesion or extension in a malignant one. Remember that the age of the tumor is more important than the age of its host.

Do not wait for a breast lesion to develop any malignant characteristics. You deprive the patient of the greatest opportunity for permanent cure by so doing.

Include in the biopsy specimen:

a. The entire palpable lesion with a wide zone of surrounding tissue.

b. The entire duct system when there is discharge from the nipple or disease of the ducts.

Examine the frozen section while the patient remains under a general anesthetic and, if malignant, proceed with radical mastectomy.

ASPIRATION IS NO SUBSTITUTE FOR SURGICAL BIOPSY

Case 7—G. E., single female, age 42. The patient discovered a slightly painful lump in the upper outer quadrant of her right breast. The next day she consulted her physician who aspirated it and informed her no further treatment was necessary. Fortunately, because the lump persisted, she consulted another physician one week later who referred her to the hospital for biopsy. Examination revealed a tender mass 1 inch in diameter without malignant characteristics in the upper outer quadrant of the breast, and the overlying skin showed considerable ecchymosis even after ten days. In addition there were multiple smaller masses in the breast highly suggestive of cystic mastitis.

Biopsy: The upper outer quadrant of the right breast was removed.

Pathologic report: Frozen section examination revealed that the palpable lump was a cyst surrounded by an inflammatory reaction, but there was also a small scirrhous carcinoma adjacent to it.

Treatment: Radical mastectomy was performed immediately. No metastases were found.

Comment: Aspiration in this case not only gave misleading information but actually caused harm by producing an inflammatory reaction around an area of cancer.

DON'T BELITTLE ANY BREAST TUMOR

Case 8—E. C., married female, age 45. The patient noticed that her left breast was gradually increasing in size, but produced no symptoms. The physician she consulted did not advise biopsy. Two years later the breast was much larger, heavy, and painful, so she sought hospitalization on her own accord. Examination revealed the left breast to be twice the size of the right and to contain a large hard mass in its outer half, fixed to the skin.

Biopsy: The tumor was widely removed.

Pathologic report: Frozen section examination showed fibrosarcoma with a degenerating fibroadenoma.

Treatment: Immediate radical mastectomy was performed. No metastases were found.

Comment: This is an example of a benign tumor which became malignant. There was sufficient warning two years previously to warrant surgical intervention at a time when the tumor might still have been benign. The delay has almost certainly precluded cure in this case.

GENERAL PRACTICE *Review*

To provide the general practitioner, as well as the specialist with concise, readily available information on the latest, proved methods of treatment of conditions commonly encountered in an average practice, POSTGRADUATE MEDICINE *offers this department to its readers. It is not, of course, intended to present these discussions as the only acceptable therapeutic procedures to be used, but rather to offer simple regimens and recommendations based on the extensive experience of the physicians who prepared these summaries.*

Management of Pulmonary Embolism

GEZA DE TAKATS

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO

In spite of the increasing awareness of subclinical and atypical forms of embolism, in spite of great interest in the prevention and early treatment of venous thrombosis, this insidious vascular accident continues to take its toll in patients who are immobilized, in cardiacs, in those harboring malignancies, in the postoperative state, and significantly enough in young, vigorous, healthy individuals in whom a pulmonary embolus is the first symptom of an acute thromboembolic disease. This often originates in a hidden, local focus and is activated by trauma, infection, or an aseptic operation.

It is quite possible that one will never be able to eliminate a certain unavoidable percentage of pulmonary emboli; nevertheless, a close study of this phenomenon is clearly indicated, since it is frequently fatal, often greatly incapacitating, and sometimes leads to erroneous diagnosis.

In the past, authors have quoted the incidence of pulmonary embolism in autopsy material, in clinical material following various disease states and operations, and have even established so-called endangered groups of patients in whom pulmonary embolism, judging from past experience and statistical data, is more frequent. In such patients prophylactic treatment has been considered; certainly, it is not feasible to treat every bedridden or operated patient prophylactically for a complication, the incidence of which has not changed in the last six years in spite of all the attention focused upon it.[1]

PROPHYLAXIS OF PULMONARY EMBOLISM

The origin of pulmonary embolism is in a localized thrombus in the peripheral venous system or in the right side of the heart. Any stagnation of venous blood in these areas predisposes to thrombosis.

For a while the overwhelming importance of the venous plexus in the foot and calf was stressed; lately it has been pointed out on good evidence that 50 per cent of pulmonary emboli originate from above the level of the inguinal ligament;[2] this means that superficial femoral vein ligations, when done for prophylaxis, will not protect patients who harbor thrombi in the large pelvic venous plexuses or in the heart. Furthermore, ligation of the superficial femoral vein in patients who are likely to get thrombosis may lead to a formation of clot, occluding the common femoral vein and thus resulting in permanent edema, induration, or ulceration.

It has been our rule always to add anticoagulants when a femoral vein is divided and gradually we have stopped prophylactic vein ligations except in patients in whom anticoagulants are not indicated, or if they have been ineffective. The only exception to this rule is when amputation of the leg or thigh is performed, where, as Veal[3] pointed out, a long venous segment is left between the origin of the superficial femoral vein and the level of amputation and where the popliteal vein is often thrombosed at the time of operation.

The prophylaxis of pulmonary embolism includes all the principles of modern surgical treatment, namely: early systematic motion in bed, elevation of the foot of the bed for better venous drainage, early ambulation, correction of blood loss, dehydration, and hypoproteinemia. With these methods alone and without the addition of anticoagulants, the incidence of thromboembolic dis-

ease has been lowered to one-third of its previous frequency.[4]

Of course, many patients cannot be mobilized and many patients suffer from cardiac decompensation, polythemia, or malignancies, which situations per se *favor thrombosis*. This term has been used frequently and is a very vague expression of what today is the crucial problem of thromboembolic disease, namely, the discovery of some simple clinical test indicating hypercoagulability of the blood. When such a finding is present, intensive anticoagulant or surgical therapy is indicated.

TESTS FOR COAGULATION TIME

Suggestions have been made to determine daily coagulation times in glass or in silicone-coated tubes, prothrombin times, heparin tolerances in vitro and in vivo, or the level of antithrombin in the blood.[5] Of these, the experience of our group has been with a simplified heparin tolerance curve, which consists of the determination of a capillary coagulation before and ten minutes after the intravenous injection of 1 cc. of 1 per cent heparin. Such a dose of heparin will result in (1) a doubling of the coagulation time—*normal reactors;* (2) more than doubling of the coagulation time—*hyperreactors;* (3) a small rise in coagulation time, less than double—*hyporeactors,* or no rise in coagulation time—*nonreactors*. While this test is only a laboratory adjunct to clinical observation, so far its simplicity and the idea that it denotes a lack of substances in the blood which activate heparin and permit its anticoagulant activity, have made us adopt it routinely to direct anticoagulant therapy.

When a patient shows a lack of response to this small dose of heparin during the first three postoperative days this seems like part of the normal postoperative state, such as elevated temperature or increased pulse rate are.[6] But after the fourth day this lack of response to heparin indicates a disturbance in clotting mechanism, which need not in itself always produce thrombosis, but which, if coupled with other factors such as prolonged stasis, dehydration, hemoconcentration, overdigitalization, and possibly others, actually develops a clinical form of thrombosis.

Needless to say, many individuals, at least half of the patients past 50 years of age, harbor small thrombi in the veins of the calf muscles, in the pelvic veins, or in any vein in the body. It is well to realize that the diagnosis of thromboembolism always denotes a clot of a certain size, and the suddenness of the occlusion with its associated reflex phenomena.

CLINICAL RECOGNITION OF PULMONARY EMBOLISM

Pulmonary embolism occurs in at least four recognizable forms and, obviously, transitions from one to another are frequent.

1. **The suspect or subclinical embolus**—Such a patient, ambulatory or bedridden, in a postoperative or postpartum state, or after a coronary thrombosis, develops a short period of dyspnea, breaks out in a sweat, exhibits tachycardia. There is no chest pain, no elevation of temperature, no roentgenologic or cardiographic changes, and the attack is over in a few minutes. There are no localizing symptoms in the peripheral veins.

Many of the associated symptoms may be due to the fear and anxiety which follow the initial vague sensation in the chest. The symptoms may never recur, but the significance of this form lies in the fact that this may be the initial small shower which is followed by a larger embolus.

If the symptoms listed are accompanied by a flat heparin curve (a nonreactor curve) heparin is immediately administered by the method to be described. If left untreated, the patient may cough up a small streak of bloodstained mucus or develop a localized pleuritic rub in which case this form merges into the second form, the small pulmonary infarct. It should be recognized that not every embolus need be followed by a hemorrhagic infarct and that quite frequently a localized patch of emphysema due to incomplete bronchial stenosis is the only effect on the lung.[7]

2. **The small pulmonary infarct**—Many of these are ignored both by patient and physician. If they are multiple and reach the visceral pleura, they are diagnosed as pleurisy, pleurisy with effusion, or virus pneumonia. Approximately half of them appear without any signs and symptoms of thrombosis. A group of these may later show clinical signs of venous occlusion in the lower extremities; in other words, the pulmonary embolus precedes the clinical manifestations of its source. The bland phlebothrombosis is the underlying cause of such emboli, which become clinically apparent on extension in the deep veins of the lower extremities.

Most frequently the right lower lobe, then the left lower lobe, the left upper lobe, and least often the right upper lobe of the lung are affected. Infarcts of the lower lobe are much more painful and present the picture of diaphragmatic pleurisy, with splinting and elevation of the diaphragm, severe pain on breathing, and shoulder pain due to irritation of the phrenic nerve. On physical examination one finds absent or diminished breath sounds, dullness on percussion, pleuritic rub, or evidence of intrapleural fluid. Then again atelectasis or atelectatic pneumonia may supervene. Certainly, the postoperative bronchopneumonia, so often feared in the past, is partly embolic in origin.

Roentgenologic findings vary from a slight elevation of the diaphragm, to emphysema, patchy or complete consolidation. The triangle-shaped infarct

is mostly absent, but occasionally recognizable on oblique or lateral film. Portable films are difficult to interpret, and one should not expect the roentgenologist to make a diagnosis of pulmonary embolism.

The volume of fluid may require tapping and if bloody fluid is found, cancer of the lung or pleura should be eliminated by stains of centrifuged specimens or thoracoscopy. Conversely, circumscribed nodular densities, especially in the upper lobe have been mistaken for carcinomatous metastases, whereas they represented repeated pulmonary emboli originating from the prostatic plexus in one of our cases.

Further diagnostic difficulties arise when a true virus pneumonia is followed by thrombosis in the lower extremities, which is not infrequent, because the development of cold-agglutinins[8] or autoagglutinins of patients affected with such a virus infection produces sludge and is a forerunner of thrombosis. Here it may be difficult to decide whether the chest findings are due to the virus infection followed by thrombosis or a thrombosis in the periphery followed by embolism. Again, if an increased clotting tendency is found, anticoagulants are in order.

3. **The massive, sublethal pulmonary embolus**—The patient is suddenly stricken with an obviously serious vascular accident. He is cold, clammy, pale, or cyanotic, and dyspnea is not as prominent as syncope. The pulse is feeble, rapid, or not palpable. The blood pressure falls or may not be measurable.

The resemblance of such a condition to a coronary occlusion is striking, and often a differential diagnosis is difficult. Roentgenologic and cardiographic studies are only worth while for comparative purposes at a later date, since four to seven days later important diagnostic help may be obtained from them. The roentgenogram will begin to show the shadow of atelectasis or consolidation after about the third day. The cardiogram, notwithstanding some authoritative statements, may be indistinguishable in pulmonary embolism from a coronary occlusion although it is true that the cor pulmonale, i.e., strain and dilatation of the right heart, does have a characteristic cardiogram.[9]

The size of the infarct, which develops in the next few days after the critical period is over, is by no means commensurate with the clinical picture. Large infarcts may give symptoms of dyspnea and cyanosis, but not the alarming collapse which can be found with small peripheral emboli. The reason for that lies in the reflex effects of small emboli in certain patients who respond to the occlusion of a small branch of the pulmonary artery with a train of symptoms which suggests a vagal effect on the heart, a bronchospasm and increased bronchial secretion, a spasm of the rest of the pulmonary vascular bed, and even more distant effects on the gastrointestinal tract, simulating gallstone colic, pylorospasm, and producing rectus rigidity.[10]

These autonomic reflexes, which are predominantly vagal, may spread to or may be carried centrally by the sympathetics, and are responsible for the symptoms of coronary insufficiency, acute bronchial asthma with atelectasis, and, most importantly, for the abdominal symptoms which have unfortunately led to emergency operations on the upper gastrointestinal tract. Coronary occlusion is well known to lead to similar pseudo-abdominal emergencies, and a chest lesion should always be excluded before needless and hazardous laparotomy.

4. **The fatal pulmonary embolus**—In our study, undertaken a few years ago with Jesser,[11] we found that patients die from a pulmonary embolus within a few minutes to several days. Patients may die suddenly while sitting up in bed, while straining during a bowel movement, and most often for no apparent cause. The rapidly fatal pulmonary embolus can of course not be treated, and the only therapeutic approach is prophylaxis. The slowly fatal pulmonary embolism, when the patient lives several hours to several days, is often treated successfully. The principles of treatment are those pertaining to the dampening of autonomic reflexes, the prevention of clot extension in the pulmonary artery or right heart, and the occasional consideration of pulmonary embolectomy.

METHOD OF TREATMENT

Only those methods used in our clinic will be described. As stated earlier, generally *anticoagulant therapy* is preferred to division of veins, the latter being used when anticoagulants fail or when they are contraindicated as in renal and hepatic insufficiencies, in hemorrhagic diseases, or in the presence of large denuded surfaces.

The anticoagulant of choice is heparin; after a test dose of 10 mg. (1 cc. of 1 per cent solution), treatment is started with 5 to 10 cc. of heparin given intravenously which should raise the capillary coagulation time from three to between eight to twelve minutes. This is a safe and effective therapeutic level which is maintained by intramuscular doses of 100 to 200 mg. of heparin (10 per cent) given every six to eight hours. A good general rule is to give 2 mg. per pound of body weight during treatment and half of this dose for prophylaxis.*

Treatment is continued until the patient is fully mobilized and leads a fairly normal ambulatory

*Recently the use of heparin in gelatin with or without vasoconstrictors has been substituted for the 10 per cent aqueous heparin. The daily dose is the same but one injection every day or every second day suffices.

existence. This may take from 5 to 14 days.

Statistics compiled by my former associate, M. H. Evoy,[12] are illuminating in that they show the number of days after operation during which pulmonary embolism can be expected. Since presumably the clot from which the embolus breaks loose is formed during or shortly after the operation, such statistics would indicate the use of anticoagulants for as long as two weeks.

The use of dicumarol has been completely abandoned for reasons which have been enumerated elsewhere.[5] Heparin therapy is controlled easily and should hemorrhage occur it can be stopped by protamine and the prompt discontinuation of the drug.

There need be no fear of increasing bloody expectoration or bloody pleural effusion following pulmonary embolism treated by heparin. As a matter of fact, it is much better for the patient to cough up some fresh liquid blood than to plug his bronchi with old clotted blood.

Since clot extension does occur after pulmonary embolism,[13] heparin will effectively inhibit it. Heparin aids in the prevention of clotting extravascular plasma in the lung and pleural fluid and thereby the absorption of pulmonary and pleural exudates is facilitated just as in thrombophlebitic edema.

If repeated emboli occur after adequate heparin therapy, division of veins is urgently indicated at as high a level as the vena cava, unless the clots are known to come from a higher level, such as after coronary thrombosis from the right side of the heart.

The dampening of autonomic reflexes—As an emergency measure to be started immediately on suspicion or diagnosis of pulmonary embolism, Jesser and I have recommended ½ gr. of papaverine with 1/60 to 1/75 gr. of atropine given intravenously together with 100 per cent oxygen inhalation by mask.[11] This will not save a patient whose both pulmonary arteries are completely occluded, but the point is that during the time of acute attack it is not possible to distinguish between complete and incomplete occlusion or small peripheral occlusion with an intensive autonomic response.

Some ill-advised emergency medication, such as morphine, epinephrine, or digitalis may aggravate the patient's response to the embolus.[10]

Papaverine will dilate the coronary artery, the spastic bronchi, and the unaffected part of the pulmonary vascular bed. Atropine will dampen the vagal reflexes. Oxygen, of course, combats asphyxia. The medication can be repeated every three or four hours, but it is needless to continue it after three days. Truly spectacular recoveries may be observed from such medication.

The patient may survive the initial vascular insult but gradually fail and die of right heart failure if the right heart is unable to maintain sufficient pressure against the increased resistance in the pulmonary bed. For such patients a pulmonary embolectomy should be tried not as an early emergency measure, but as a deliberate procedure on the second or third day, with evidence of a falling arterial and rising venous pressure. Such cases will obviously be rare, because patients either die or recover from the pulmonary embolus, but for the slowly fatal type the approach of Neuhof[14] through the right ventricle should be kept in mind. Our service is trained for this method but no suitable case has yet been encountered; it should be done neither too soon nor too late.

SUMMARY

Pulmonary embolism is an important vascular accident which should be suspected, recognized early, and intensively treated. Its prophylaxis lies of course in the prevention of thrombosis, which follows a number of disease states, operations, or childbirth.

Conditions favoring thrombosis and coagulation studies detecting an increased clotting tendency are under intensive study. When the embolus occurs it may be subclinical or suspect, manifest itself in a small pulmonary infarct, in a massive, sublethal form, or be fatal. The fatal embolus may kill instantly or slowly.

The method of treatment consists of emergency measures to combat autonomic reflexes, anticoagulant therapy with heparin, and an occasional embolectomy.

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Treatment of Thermal Burns

RICHARD W. VINCENT

NEW ORLEANS

When one thinks of burns as being treated by a plastic surgeon, he generally considers that the ones included are those which are very serious and require plastic surgery. There are certain principles which have been worked out in the treatment of severe burns which, when applied, may prevent the need for plastic surgery.

There is little problem in making a diagnosis; however, there is a problem in estimating the depth of the burn. An adequate history will give the nature of the burning agent and the time that it was in contact with the skin. Physical examination will determine the presence or absence of blebs and the color and consistency of the skin. A slate gray or leathery skin is generally associated with a deeper burn. The temperature of the burning agent, the specific heat of the object, and the time in contact determine the depth.

Certain specific types of burns require different therapy, but in general the principles discussed here apply to all burns, particularly thermal burns, which are the most common.

The eventual disability resulting from a burn is determined by its depth and by the treatment received. Treatment presents two problems, the general and the local. Both are important. Actually they cannot be completely separated.

GENERAL THERAPY

The immediate problem is treatment of shock, if present, and the relief of pain which is actually a part of the treatment of shock. In adults the author prefers morphine used intravenously. This has the distinct advantages of rapidity of action and less likelihood of overdosage. Morphine administered to a patient in shock may not be absorbed. If the circulation improves following repeated doses of morphine, the total accumulated dose is made available. This is then absorbed, giving an overdose, which may cause respiratory distress. The routine used is ¼ gr. of morphine dissolved in 2 cc. of distilled water administered slowly, until the patient states that the pain is less. Most patients will require less than ¼ gr. of morphine.

Shock is treated by the usual measures. Hemoconcentration is corrected. Whole blood, blood and saline, or blood plasma may be used. It is not within the scope of this article to set up standards for the quantity to be given. Good authority can be quoted for almost any combination and amount of fluids, plasma, and blood. To treat immediate burn shock as any other type of shock may simplify the treatment for the man who does not see many burns but is accustomed to seeing traumatic cases.

LOCAL THERAPY

When the pain has been relieved and the blood or plasma, if indicated, has been started, local therapy is begun. General anesthesia, scrubbing with a brush, and the use of tincture of green soap are condemned. Adequate cleansing is possible without anesthesia after morphine has been given. A gentle cleansing is done with water, sterile cotton, and a mild, white bar soap. Recently pHisoderm has been used. The amount of cleansing done is governed, to some extent, by the severity of the burn. In very extensive burns little or no cleansing may be indicated. In less extensive burns, or those of an important area, it is best to do a more thorough cleansing. Blebs may be opened and skin tags cut off; however, no attempt is made to peel the entire burned area. This cleansing should be done rapidly and efficiently. If this is not possible, little or no cleansing may be indicated.

Following cleansing the dressing is applied. The first layer should be fine mesh (44 x 40) gauze, plain, or covered with vaseline or a mild ointment. Some authorities use a fine grade rayon.

It must be stressed that little can be accomplished by the use of local medication. Actually, an overdose of certain drugs may be received from their application over too great an area. Several layers of regular gauze are then applied. Over the regular gauze mechanics waste, colostomy pads, or five-yard rolls are applied in sufficient amounts to give a dressing about an inch thick. The area is then wrapped with Ace bandages. Care is taken that the dressing is snug but that it does not interfere with circulation. Plaster splints to extremities will give support and prevent movement. Circular plaster casts may be dangerous when they are applied to a burn.

To prevent infection, antibiotics are given. Sulfonamide drugs are now rarely indicated.

SUBSEQUENT THERAPY

Beginning at once, the patient should receive adequate nutrition. The protein intake is particularly important. Feeding is supplemented by vitamins and high protein drinks. Once the hemoconcentration has been corrected, the patient must be watched to prevent the occurrence of anemia. This is less likely to occur with the early use of whole blood.

After five to fourteen days the dressing is changed. On burns which have been cleansed, the dressing may be left in place for a longer period. When less complete cleansing has been done, at least the outer layers may be changed within one week. Between the tenth and fourteenth days it will be much easier to determine the depth of a burn. At this time the problem of whether or not a skin graft is indicated can be decided and a plan made for the further handling of the case.

The problem will arise as to whether or not the patient should be hospitalized. The need for hospitalization is determined by location of the burn and percentage of body surface involved. It is rather important to obtain a maximum good result where the face, hands, and feet are involved. Burns of the face are best treated in the hospital. A good cosmetic result is desired, the dressing must be changed more often, and there is the added safety factor. Flame burns of the face and neck may produce respiratory obstruction due to swelling of the neck or edema of the mucous membrane of mouth, pharynx, and glottis. Tracheotomy may be found necessary.

The author has used the above methods in treating a rather large series of burns on an ambulatory status. The first dressing is applied in the hospital. Subsequent dressings are done either in the hospital or office. Certain patients, particularly children, are treated the first few days in the hospital, and discharged when it is seen that there is no severe systemic reaction.

Laboratory Procedures in the Diagnosis of Hyperthyroidism

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A careful history and physical examination constitute the basis for the diagnosis of hyperthyroidism. Nevertheless, they do not always enable the clinician to distinguish between this disorder and the various conditions which may be confused with it. The determination of the basal metabolic rate and of the total serum cholesterol are then usually resorted to but frequently may not clarify the situation. A therapeutic trial with iodine or antithyroid drugs may finally be undertaken.

Recent work has provided two laboratory procedures which appear to offer greater accuracy in the estimation of the level of thyroid activity. One is the measurement of uptake by the thyroid of tracer doses of radioiodine,[1-3] and the other, the chemical determination of the serum precipitable fraction of the blood iodine.[4,5]

BASAL METABOLIC RATE

The basal metabolic rate is an expression of caloric output, as estimated from a measurement of oxygen consumption after the subject has fasted for twelve to eighteen hours. The patient must be at absolute rest, but not asleep. The oxygen uptake thus determined is related in turn to surface area and is used to express the caloric requirements for the basic metabolic processes of the body apart from muscular activity. The basal metabolism is calculated as a percentage of a standard previously and empirically determined for age and sex. Excitement or muscular activity just before or during the test will, therefore, negate one of the prime conditions of the definition, that the patient be absolutely at rest. Such inability to relax, or persistent nervous motions may result in an increased oxygen uptake, but this increased value is not a reflection of "basal" requirements, but rather of the added muscular exertion.

Deliberate interference with breathing patterns, so that the expiratory position of the chest is appreciably changed during the test, may alter the apparent amount of oxygen used. This may produce extremely low or high values for the basal metabolic rate, which again are entirely false. Thus,

values of +90 per cent or more have been produced at will by normal subjects trained to breathe improperly. The changes in chest volume thus produced imitate the respiratory alterations unconsciously shown by the nervous or hysterical patient. Also, emotional disturbances may produce frequent sighing and other irregularities in the spirogram which may make it impossible to establish the trend of oxygen consumption from which to make subsequent calculations of the basal metabolism.

Unfortunately, there are still other causes for false values for the basal metabolic rate. Oxygen consumption, as measured during a basal test, is referred to the surface area of the individual in order to calculate the basal metabolism. An error in the estimation of the surface area may lead to a significant discrepancy in the calculated basal rate. Errors in the formula for estimating surface area are relatively frequent, especially in children and in obese and very thin adults. Mechanical defects, such as leaks and faulty carbon dioxide absorption, may lead to erroneous results. Moreover, an increase in metabolic rate may be found as part of the disease and unrelated to thyroid overactivity in many patients with hypertensive disease, dyspnea due to cardiac or pulmonary failure, paralysis agitans, leukemia, and some of the other lymphomata. On the other hand, physiologically lowered oxygen consumption occurs if the patient falls asleep during the test.

FASTING SERUM CHOLESTEROL TEST

The results of the fasting serum cholesterol determination also require scrutiny. First, various methods for the estimation of this serum component are in use, and provide different ranges of normal values, as well as variable accuracy in reproducibility of results. Second, the cholesterol level of the serum is only indirectly a measure of thyroid function. Thus while an increase in circulating thyroid hormone tends to lower the serum cholesterol, and a decrease to elevate it, the correlation is only approximate. The various mechanisms of regulation have not been entirely elaborated.

It is clear that the nutritional status, the degree of pituitary and adrenal activity, and the presence of various disorders, apart from thyroid disease, such as diabetes mellitus, also may affect the cholesterol content of the serum. Finally, a single cholesterol determination may be valueless in making a diagnosis of hyperthyroidism, since the cholesterol in toxic goiter is not as consistently reduced below the wide range of normal values, as it is elevated above these limits in hypothyroidism. Nevertheless, a series of determinations may be useful in following fluctuations in thyroid activity.

RADIOIODINE TRACER MEASUREMENT

The recently introduced procedure of measurement of uptake of tracer doses of radioiodine does provide a direct test of thyroid function. Such uptake by the thyroid can be reasonably well correlated with glandular activity.[6] Small tracer amounts of I^{131}, generally 40 microcuries, are given by mouth dissolved in water. There is practically no stable iodine in this material and so no biologic effects result from the iodine, apart from its radioactivity. A Geiger counter with a wide aperture is placed at a standard distance from the thyroid gland and is used to measure the amount of isotope accumulated by the gland, as determined from gamma ray radiation. Such measurements are generally conducted twenty-four hours after the administration of the I^{131}, unless the rate of accumulation of iodine is determined,[7] in which case uptake is generally tested between two and six hours after ingestion.

The normal I^{131} uptake at twenty-four hours ranges from 10 to 40 per cent of the ingested dose. The estimation of urinary excretion of I^{131} after oral administration[8,9] has been used as an alternative to direct measurement over the gland, but is subject to errors of collection often unknown to the clinician. Recent administration of stable iodine, such as with dyes for intravenous pyelography and cholecystography, or Lugol's solution, thyroid medication, or antithyroid drugs may inactivate I^{131} uptake for from two to twelve weeks. A brief history before the test is performed should avoid errors from this complication. Finally, previous therapy, as with operation, may alter the usual relationship between iodine uptake and hormone secretion and render the results of the test invalid.

A study was recently made on the wards of the Presbyterian Hospital of the possibility of routinely using the tracer technic to replace the basal metabolism as an exclusion test for thyroid dysfunction.[10] One hundred seventy-five patients, for whom basal metabolism tests had been ordered to rule out thyroid disorders, were concurrently given I^{131}. Of these, 125 were subsequently shown to be euthyroid. About 45 per cent of all basal metabolism values in this euthyroid group exceeded the limits of ±10 per cent, and 33 per cent were beyond the limits of ±15 per cent. About 25 per cent of the basal metabolism values in the euthyroid group were higher than +15 per cent. The radioiodine uptake in the same group showed about 10 per cent of values to be in excess of the normal upper limit of 40 per cent uptake. There was only 1 value beneath the normal lower limit of 10 per cent uptake. Thus, most of the errors were on the high side, and overlap with the lower limit of uptake values seen in hyperthyroidism.

Six per cent of readings in toxic goiter fall within the normal range of uptake. However, values for uptake of 50 per cent or more appear to be pathognomonic of toxic goiter or some other

thyroid disturbance. The tracer test is not influenced by emotion, ingestion of food, or muscular activity as is the basal metabolism test. Also, the procedure is more acceptable to the patient, and technician capacity is considerably greater than with the basal test. These advantages, plus the 85 per cent accuracy of the tracer procedure, suggest that the first appraisal of thyroid function might well be made by this method. Abnormal values, or discrepancies from clinical judgment, would then be confirmed by other procedures, rather than using the other tests first and confirming these with the tracer as is generally done at present.

Refinements of this tracer technic already have been appearing and may eventually eliminate or greatly narrow the percentage of the present method. Thus, partitioning of the serum to determine the extent to which ingested radioiodine subsequently appears in the hormonal organic iodine fraction of the serum,[11] appears to offer promise. Such studies reveal a greater percentage of the I^{131} in this serum precipitable form in hyperthyroidism than in normals, at a given interval after ingestion.

Another interesting approach has been the calculation of radioiodine clearance rates by the thyroid.[12] This technic involves both a determination of the rate of accumulation of the isotope by the gland, and a knowledge from blood samples of the level of the radioiodine in the serum. The clearance rate is greatly exaggerated in toxic goiter. The modifications of the direct measurement of uptake over the gland require wider application before it is clear whether they eliminate error and can be used routinely.

SERUM PRECIPITABLE IODINE

The second objective and direct test of thyroid function recently introduced is the chemical determination of the level of serum precipitable iodine. This test avoids the inaccuracies inherent in determining total serum iodine since only the organically bound fraction is measured. For example, iodine inhaled by the patient is not a source of error, as it may be with the total iodine test. A normal range of 4 to 8 gamma per cent has been determined. However, there is no consistently sharp demarcation between the values found in normal and hyperthyroid patients. Borderline levels occur and may occasionally be difficult to interpret. Moreover, the test requires an exacting, precise technic, and is not readily adaptable to routine use.

The role of this method, at present, is as a confirmatory procedure when the other methods have failed or provide conflicting results, or when investigative studies are being pursued. However, the intelligent application of both the radioiodine tracer technic and the chemical determination of serum precipitable iodine has led to a degree of accuracy in the diagnosis of thyroid disorders that is considerably higher than any hitherto realized.

SUMMARY

1. A brief description is presented of the limitations of the basal metabolism, fasting serum cholesterol, radioiodine tracer, and serum precipitable iodine technics in the diagnosis of hyperthyroidism and other thyroid disorders.

2. It is suggested that the radioiodine tracer test be used as an exclusion test for abnormal thyroid function instead of the basal metabolic rate determination.

3. A combination of the radioiodine tracer method and the determination chemically of the serum precipitable iodine level has given a high degree of accuracy in diagnosis.

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EDITORIALS

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INDEXING OF MEDICAL LITERATURE

Most desirable as a time-saving tool for those devoted to basic scientific research in the field of medicine and to clinicians would be a monthly index of the important medical literature of the world with subjects and authors arranged alphabetically in a single index—the whole accumulated at least annually and possibly also for five-year periods. The desirability of such an index has been long recognized—certainly since the time when John Shaw Billings first established the Index Catalog of the Army Medical Library and the Index Medicus.

Today the significance of such a contribution to medical research has been so definitely recognized that the U. S. Army has established a research project under Dr. Sanford Larkey, librarian of the Welch Medical Library of Johns Hopkins University School of Medicine to determine the periodicals most important, the fields that they cover, and the most effective technics for indexing of subjects. The National Research Council has established a Committee on Indexing under the chairmanship of Dr. Chauncey Leake, vice president of the University of Texas and dean of the school of medicine. This committee likewise is studying the scope and other factors concerned in medical indexing.

The extent of the problem may be estimated from the fact that there are about 10,000 medical periodicals which appear throughout the world. The Army Medical Library receives about 7,000 of these periodicals, of which something under 2,000 are now indexed in the monthly periodical published by the Army Medical Library called "The Current Medical List." This Current Medical List provides the tables of contents of the leading medical publications of the world and with them a subject index. The subject index of the Current Medical List will be cumulated at least annually.

The Quarterly Cumulative Index, begun experimentally as a project of the American Medical Association in 1916 and later incorporating the Index Medicus to form the Quarterly Cumulative Index Medicus, is unfortunately no longer quarterly or cumulative and even more unfortunately now appears so late as to seriously embarrass those engaged in medical research who depend on it as a source of information on current progress in medical research. The Quarterly Cumulative Index Medicus has usually indexed some 800 periodicals almost fully and an additional 400 partially.

Excerpta Medica, published in Amsterdam in English, now covers some 2,000 medical periodicals and prepares from them some 70,000 abstracts annually. In this great venture some 4,000 physicians collaborate.

At the meeting of editors of medical journals from various nations associated with the

World Medical Association in New York City the subject of medical indexing and abstracting was given special consideration. All of the world must probably depend today on the American medical profession to provide it with bibliographic material as an important accessory to research. Some nations now publish indexes to their own literature—notably Russia and Poland—but world literature includes many nations which publish but a single medical journal, others which publish from 50-100, and nations like the United States with almost 350 important medical periodicals. No one knows when or where a single medical contribution may some day appear which might revolutionize the diagnosis, control or treatment of a serious disease.

The importance of widespread dissemination of medical literature has been recognized by such agencies as the World Health Organization and the World Medical Association and a definite portion of the funds of the National Science Foundation will be allotted to such projects. Certainly the time has come when every agency concerned with this matter may well enter into an international cooperation leading toward the best possible result that can be accomplished.

MORRIS FISHBEIN

A HEART HOSPITAL FOR MINNESOTA

On the campus of the University of Minnesota, closely integrated with the medical school and with the facilities for graduate education, now rises a modern hospital devoted to research on diseases affecting the heart and to the care of patients with heart disease. Among the appropriations which have served to develop this institution, probably the best of its kind in the United States, were a contribution from the Variety Club of the Northwest of $400,000 and a grant from funds developed under the Hill-Burton Act and an appropriation from the state of Minnesota, as well as individual contributions by people and industries of this great state.

Rheumatic fever in children is still the leading cause of death between 5 and 15 years of age. From ages 15 to 25 years rheumatic fever is outranked only by tuberculosis. Conservative estimates say that 500,000 children in the United States have rheumatic fever. A few other leading institutions in our country also devoted to the care and study of this disease are Irvington-on-the-Hudson and the St. Francis Sanitarium in Brooklyn, and the La Rabida Sanitarium in Chicago. In the great medical center at Bethesda a special hospital is under construction which also will be concerned with heart disease.

Today diseases of the heart are first in the list of causes of death; they will no doubt continue to occupy that position from this time onward. The heart begins to beat before the birth of the child and carries on until the moment of death. Hardening of the arteries and high blood pressure contribute largely to the deaths of people of advanced years. Coronary thrombosis, secondary to these conditions, has come to be feared as the sudden death that strikes men who are leaders in industry, in the professions and in statesmanship.

The new hospital will have 40 beds for children and 40 for adults; it will include an outpatient department for nonhospitalized cases. Lounges and sunrooms will be available to aid the long convalescence usual in diseases of the heart; a spacious auditorium for 100 spectators (especially a project of the Variety Club) will have room for wheel chairs and litters.

The Variety Clubs elsewhere in the United States have distinguished themselves by their contributions to medical purposes. Founded in Pittsburgh to care for a little child abandoned in a motion picture theater, Variety Clubs have spread throughout the nation. With the problems of little children chiefly their objective, they represent a typical American activity. Membership is voluntary and philanthropy is incidental but, at the same time, the chief motivating force of these groups.

The building of this great hospital for the

heart, closely integrated with the University of Minnesota and its medical school, is in the best American tradition. The citizens of a free country must assume as far as they possibly can the responsibilities for their progress.

MORRIS FISHBEIN

MEDICINE IN PUBLIC AFFAIRS

Since 1913 the medical profession of the United States has waged a continuous campaign against nationalization of medicine and the establishment of government controlled medicine for all the people of the United States. The issue became definitely political with the establishment of the Social Security Board in 1935. Legislation designed to make insurance against sickness compulsory for all employed workers in the United States, largely inspired by employees of the Federal Security Agency, has been before the Congress and the Senate continuously since that time.

Recognizing that need for insurance exists, nonprofit and private insurance against the costs of hospitalization and medical care has been developed over a period of 20 years. Now almost 70,000,000 people in the United States are insured against the costs of hospitalization; the number insured to a greater or lesser degree against the costs of medical care is continually increasing.

The medical profession has determined that the widest possible coverage by voluntary sickness and hospitalization insurance will so thoroughly meet the needs of the people of a democratic government that the care of the neglectful and of the totally or partially indigent will not be too great a problem but can be met by local and state agencies with national financial aid. The enactment of the Hill-Burton legislation aiding the individual states in building hospital facilities and health centers has been a fundamental step toward recognition of local responsibility and the value of local administration.

Today the nation is still confronted with a powerful movement in behalf of nationalized medicine, largely supported by two elements in the population—much of unionized labor and the social and welfare workers. The drive in behalf of such legislation was given increased impetus with the election of the present Democratic administration and suffered a considerable setback in the elections of 1950. The exigencies of war have called a halt to the powerful propaganda exerted by governmental political agencies. The threat of such legislation is likely to be less until the subject becomes a major political issue with the election of a president in 1952.

The most important single measure toward meeting this problem is better education of the mass of the people as to the significance of the movement, to the dangers inherent in the delegation of such responsibilities to the federal government, the danger of establishing and erecting a vast bureaucracy which becomes potentially a political threat, the danger of tremendous misuse of medical services and wastage of medical facilities clearly apparent in the lamentable British experiment. Emotional appeals during elections are useful but firm conviction comes only with complete understanding.

MORRIS FISHBEIN

PROGRESS AGAINST CORONARY THROMBOSIS

If there is one group in the United States that is more concerned than any other with coronary thrombosis, that group comprises the medical directors of the great life insurance companies. In a recent meeting of these directors Dr. Roy W. Scott, professor of medicine at Western Reserve University, ascribed the incidence of coronary artery disease to the general pattern of the coronary arteries with which one is born.

In a series of cases of occlusion of the coronary arteries seen in the Johns Hopkins

Hospital, Andrus found that the mortality rate among private patients was 18 per cent compared to nearly 30 per cent among patients in the wards. He ascribed this difference to earlier diagnosis and hospitalization for the private patients.

Two medical directors—Drs. Waldron and Constable—had studied the records of 1,551 cases of myocardial infarction which had survived three months or longer. Among people in the 30-39 age group, the average life expectancy was 11½ years; for those 40-49 years of age, it was 10½ years, and for those in the 50-60 year age group, it was 8½ years. The highest mortality was found among persons with complications and with pre-existing associated defects. Significant was the opinion of Doctors Waldron and Constable that electrocardiographic studies do not appear to have great prognostic value.

Some hope in coronary thrombosis, as well as in other thromboembolic diseases, rests on the use of anticoagulant drugs accompanied by tests of the blood clotting time with various simplified new procedures that are now available. Several tests have been devised for determining prothrombin activity. These tests have now been so simplified that they can be made by any practitioner who has studied the test and developed some experience. These tests permit use of anticoagulant drugs with proper control as to the amounts to be given, thus avoiding the possibility of dangerous hemorrhage. The prothrombin test is also used in cases of hepatitis, poisoning and toxic effects of radiation.

Progress against coronary thrombosis continues. The time may yet come when it will be possible to indicate those most likely to suffer this dangerous cardiovascular accident and to take measures with some certainty of prevention.

MORRIS FISHBEIN

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The Medical Bookman

THE EYE MANIFESTATIONS OF INTERNAL DISEASES*

This book was written for the ophthalmologist as well as others engaged in either general or specialized practice. The first five chapters are obviously intended for student beginners and those without special training in ophthalmology. The normal anatomy of the eye is described somewhat briefly, but adequately. There is a discussion of the causes of eye manifestations and a short description of the examination of the patient which includes some of the routine tests, methods, instruments and equipment used. Two of these chapters are concerned with structural abnormalities and manifestations.

The second portion of the book begins with the sixth chapter entitled, "Congenital and Hereditary Eye Manifestations." The chapters on Infections and Infectious Diseases describe the eye manifestations of all the acute and chronic infectious diseases with separate chapters devoted to syphilis and tuberculosis. Other infections are grouped as Virus and Related Infections, Fungus Infections and Focal Infections. The ocular findings of the more important Drug and Chemical Intoxications are also described.

The remaining chapters are devoted to the eye manifestations of nearly every disease and system of diseases. These include Diseases of the Cardiovascular System, Diseases of the Blood, Disorders of Menstruation and Pregnancy, Diseases of the Endocrine Glands and Metabolism, Avitaminosis and Diseases of Nutrition, Diseases of the Nervous System, Intracranial Tumors, Diseases of the Skin and Diseases of the Bones of the Skull and Orbit. In these chapters a brief preliminary description of the primary or systemic disease is included. The more important ocular manifestations are described in detail with special reference to the appearance, differential diagnosis, management, treatment and prognosis of the condition wherever possible.

Many new and pertinent illustrations have been added to this edition. The section on glaucoma has been entirely rewritten to conform with the present understanding of this condition as elaborated by the Symposium on Glaucoma at the meeting of the American Academy of Ophthalmology and Otolaryngology in October, 1948. The new material includes such diseases and syndromes as retrolental fibroplasia, Harada's disease, Behcet's syndrome, rubella, acute anterior poliomyelitis, vascular encephalotrigeminal syndrome (Sturge-Weber), Sjögren's syndrome, Hutchinson's syndrome, malignant exophthalmos, cranial arteritis, scrub typhus and psychosomatic disorders.

An attempt has been made to include the most recent forms of treatment wherever possible.

In the first part of the book, Chapter III is devoted to the Examination of the Patient. This chapter is extremely well done, with proper emphasis placed upon the value of general inspection. The importance of an accurate history and record of the case, as in other branches of medicine, is also emphasized. It is noted that many of the functional tests are made with precision instruments and can be repeated under similar conditions giving results whose comparison is of great value.

Chapter VII, in the second portion of this text, describes the ocular manifestations of many infections and infectious diseases. The author feels that the most common form of ocular involvement in scarlet fever (scarlatina) is hyperemia of the conjunctiva and conjunctivitis. In whooping cough (pertussis) the eye manifestations are few in number and severity and include, principally, hemorrhages which occur in the conjunctiva and eyelids. Ocular findings are not frequent in typhoid fever, but ulcers of the cornea may occur as well as iritis, metastatic choroiditis and optic neuritis.

Almost any of the ocular structures may become involved during or following an attack of influenza (la grippe) and about 7 per cent of the cases show manifestations in the eye. Conjunctivitis is the characteristic lesion in diphtheria (membranous croup) and two forms are to be distinguished—a superficial or croupous form and a deep form. Erysipelas (St. Anthony's fire) of the face may be considered in great part to be a disease of the eyelids. The eye manifestations of gonorrhea, says the author, may occur in one of three forms: gonorrheal ophthalmia (gonorrheal conjunctivitis), ophthalmia neonatorum and metastatic gonorrheal ophthalmia.

In leprosy (lepra arabum) 13 per cent to 29 per cent of the patients are blind in one or both eyes as a consequence of ocular involvement; superficial punctate keratitis or pin-point lepromata of the irides is so typical as to be diagnostic of ocular leprosy. Edema of the eyelids with subsequent vesiculation, crusting and occasional disfiguring scar formation are characteristic of anthrax. Un-

*The Eye Manifestations of Internal Diseases (Medical Ophthalmology). By I. S. Tassman, M.D., Associate Professor of Ophthalmology, Graduate School of Medicine, University of Pennsylvania, Philadelphia; Attending Surgeon, Wills Eye Hospital, Philadelphia. Ed. 3. 672 pages, with 279 illustrations, 25 in color. 1951, The C. V. Mosby Company, St. Louis. $12.00.

FIGURE 10. Exophthalmos. Note the more marked protrusion of the right eye with widened palpebral fissure and anxious expression of the patient. (I. S. Tassman, Wills Hospital.)

(Illustrations from Tassman: Eye Manifestations of Internal Diseases.)

FIGURE 166. Gumma of right orbit. (I. S. Tassman, Wills Hospital.)

FIGURE 167. Same patient shown in FIGURE 166 after receiving specific treatment.

dulant fever (brucellosis, Malta fever) may affect the extra-ocular muscles, the cornea, the uveal tract, the retina and the optic nerve. Tularemia is recognized as an oculo-glandular syndrome which is characterized by a glandular swelling accompanied by a nodular form of conjunctivitis.

In Chapter VIII the important disease, syphilis (lues), is discussed in minute detail. Among the ocular manifestations described are syphilis of the orbit, ocular muscle palsies, the Argyll Robertson pupil, lesions of the eyelids, syphilis of the conjunctiva and sclera, corneal involvement, iritis and iridocyclitis, choroiditis, uveitis, retinitis and syphilis of the optic nerve.

In the final portion of the book the author introduces Chapter XVII entitled "Disorders of Menstruation and Pregnancy," with the statement that "The numerous and complex possibilities concerned with the normal and altered function of the female generative organs obviate any detailed discussion of the subject in this instance." Nevertheless he does cover the subject very well. He states that during menstruation edema of the eyelids and blue rings are often present and these usually clear up later. Evans has found a wedge-shaped scotoma with its apex at the blind spot and its base directed peripherally to be present frequently. Others have detected enlargement of the blind spots and temporary contraction of the peripheral fields during menstruation. Amenorrhea may be accompanied by a sensation of heaviness and fullness about the eyes. Small retinal hemorrhages and acute retrobulbar neuritis may occasionally occur. Vicarious menstruation in the form of subconjunctival hemorrhage has been reported by Poos. Metrorrhagia may be accompanied by migraine and transient amaurosis. In cases of uterine hemorrhage ocular manifestations may appear, usually in both eyes, characterized by sudden loss of vision and the presence of an optic neuritis or neuroretinitis.

According to the author, it is felt that during pregnancy there is a physiologic enlargement of the pituitary gland which presses upon the chiasm and produces the changes in the optic nerve and in the visual fields which frequently occur. The optic neuritis which occurs has been attributed also to the effect of toxins. The occurrence of hemorrhagic retinopathy with severe vomiting of pregnancy, says the author, is significant of a bad prognosis and an indication for therapeutic abortion.

The retinal changes in toxemia of pregnancy are of utmost importance from a diagnostic and prognostic standpoint. The earliest visible sign of toxemia is attenuation of the retinal arterioles and is noted about the time the diastolic blood pressure reaches 95 mm. of mercury. As the narrowing becomes marked, areas of angiospasm occur in which the blood column can no longer be distinguished. These signs constitute the "preorganic stage" and with the proper management many of the cases progress no further. However, when the condition is persistent over a long period of time it leads to the presence of sclerosis and the introduction of the "organic stage" of the disease. When the sclerosis is followed by the appearance of hemorrhages, exudates and edema in the retina the picture then constitutes a retinopathy of toxemia of pregnancy. An occasional complication of toxemia of pregnancy is detachment of the retina which, however, returns to normal after recovery from the toxemia.

Puerperal septicemia may result in a metastatic choroiditis or retinitis and retinal hemorrhages. In normal or prolonged lactation an optic neuritis may occur about the seventh or eighth week, but this can be terminated by weaning.

P. B. J.

► A TEXTBOOK OF VENEREAL DISEASES - - -

By R. R. Willcox, Consultant in Venereal Diseases, St. Mary's Hospital, London; Physician-in-Charge, Venereal Diseases Department, King Edward VII Hospital, Windsor. 439 pages, with 154 figures. 1950, Grune & Stratton, Inc., New York. $5.00.

This text presents a complete discussion of all the venereal diseases commonly encountered in this country. Also included are those diseases of a related nature found in other regions of the world. In addition to a concise and clearcut description of the anatomy involved, the symptomatology, clinical characteristics and complications of each disease are presented in an easy and readable manner.

The various laboratory technics involved in confirming the diagnoses are also included. Stress is placed on the differential diagnosis of syphilis and allied diseases, as well as that of gonorrhea and nonspecific urethral discharges. Excellent illustrations facilitate reading and understanding.

The sections dealing with therapy include the most recent drugs and current courses of therapy considered most effective in the early, intermediate and late stages of syphilis are outlined in an easily understood fashion.

This book may well be considered a valuable addition to the library of the general practitioner, as well as to the specialist who encounters these diseases in the field of his choice.

R. A. W.

► A SHORT TEXTBOOK OF RADIOTHERAPY - - -

By J. Walter, M.A., B.M., M.R.C.P., D.M.R.E., Deputy Medical Director, Sheffield National Centre for Radiotherapy, and H. Miller, M.A., Ph.D., F. Inst. P., Physicist, Sheffield National Centre for Radiotherapy. 444 pages, with 199 illustrations. 1950, The Blakiston Company, Philadelphia & Toronto. $6.00.

This excellent text is primarily intended for radiotherapy technicians and students. A great need for such information has been long needed. The text can be fundamentally divided into three portions. The first, which deals with physical properties of x-ray and radioactivity, is extremely well written and easily understood by a novice in the field. In fact, this portion of the book can well be recommended to physicians who are interested in this subject and to medical students.

The section on biology and pathology has been written in a manner usually presented to nurses in training and is, therefore, extremely elementary for medical men.

The third section, describing methods of treatment, is quite general, and many of the generally accepted variations in radiotherapy are described. The reader must remember that the methods mainly described herein are those in use at the institution in which the authors are active and that the methods used at the various institutions in this country will not coincide with those described. A special condensed chapter for dermatologists using radiotherapy is included.

This book would be a valuable adjunct in any x-ray department for reference by technicians, students in technic and early students of radiotherapy.

J. F.

► ANXIETY IN PREGNANCY AND CHILDBIRTH - - -

By Henriette R. Klein, M.D., Associate in Psychiatry, Columbia University College of Physicians and Surgeons, New York; Howard W. Potter, M.D., Professor of Psychiatry, Long Island College of Medicine, Brooklyn; and Ruth B. Dyk, M.S., Research Department, New York City Youth Board. 111 pages. 1950, Paul B. Hoeber, Inc., New York. $2.75.

This monograph represents the results of a study made of the psychosomatic relationships during pregnancy and childbirth in a group of 27 primiparous women at the Long Island College Hospital. The patients were young healthy women of marginal social and economic status with few or no intellectual interests. Three-fourths of the group had grown up in unstable environments and broken homes which may explain why the group was also heavily weighted by marital uncertainty or dissatisfaction.

The authors, two psychiatrists and a psychiatric social worker, present in detail the results of interviews made during and after pregnancy. They attempt to correlate social and economic background, attitudes toward conception, anxieties, sexual adaptation during pregnancy, physical symptoms, and behavior in pregnancy and parturition.

Several positive deductions are made from this study. The combination of unfavorable economic factors together with unfavorable marriages discouraged positive attitudes toward conception in all instances. While strong feelings for or against pregnancy were maintained throughout gestation, ambivalent attitudes seen early in pregnancy were usually resolved in favor of acceptance as the pregnancy progressed. In no case was the child rejected because of its sex. No significant change occurred in sexual response during the pregnancy period. Sexual inhibition which was characteristic of this group was related to an adverse attitude toward nursing. Anxiety about pregnancy or childbirth was found in every patient. An emotionally unstable woman needs particular attention for her fears and anxieties to relieve the stress and strain she is apt to have during pregnancy. Nausea and vomiting, in contrast to other physical symptoms, were not found to be an index of either the degree of stability or how much the child was wanted. A woman with a stable personality was inclined to react well psychologically during labor whether it was easy or difficult while the unstable patient, although likely to react well if labor was easy, reacted badly when labor was difficult.

The authors believe that this study brings into focus significant points which need continued scrutiny. Among these points they modestly include the possible emotional effects of being the subject of an investigation.

M. B. S.

► TECHNIQUES IN BRITISH SURGERY - - -

Edited by Rodney Maingot, F.R.C.S. 734 pages, with 473 figures. 1950, W. B. Saunders Company, Philadelphia & London. $15.00.

This book represents a collection of papers written by a number of leading British surgeons who have obtained recognition in the fields of surgery upon which they have written. The contents of the book cover all of the regions of the body which might be considered within the field of the general surgeon.

The book has been well published and carefully edited. The illustrations throughout have been excellently done and are pertinent to the subject material.

Part I, dealing with the head and neck, covers the fields of head injuries (Rowbotham), spinal tumors (Rogers), the thyroid gland (Piercy) and the surgery of Parkinson's disease (Oliver) in a manner such that the reader recognizes that the authors have had sufficient experience to make a difficult problem appear simple.

Part II, directed to thoracic surgery, includes a discussion of congenital heart surgery (Mercer) with well chosen diagrams and sketches to illustrate the abnormalities and pertinent phases of surgical technic. Other subjects in this section are the removal of the thymus gland for myasthenia gravis (Keynes), the various phases of pulmonary surgery (Barrett, Sellors, and Thomas), and the field of mammary plasty (McIndoe). Each article is sufficiently detailed to serve adequately for the student who wishes to review the principles of diagnosis, treatment and surgical technic.

In part III, surgery of the stomach and bowel has been discussed by such men as H. D. Johnson, Aird, Norbury, Tanner, Monro and others. Johnson indicates that the abdominal approach for vagotomy has many advantages over the thoracic approach.

Maingot has written the section on various phases of cardiospasm and its treatment, pointing out that approximately 70 per cent of the cases can be cured with the hydrostatic bag. The physical approach and technic for the operative cure of cardiospasm have been carefully described and illustrated.

Part IV deals with problems of orthopedic surgery, infections of the hand and the problem of senile and diabetic gangrene of the extremities.

Maingot has done a creditable job of compiling, in more or less textbook fashion, the important problems of the general surgeon, in such a way that the book can be used either by the student who is interested in learning his fundamentals or by the surgical clinician as a reference book for modern surgical procedures.

A second edition can be visualized wherein other authors might also be used to keep the material constantly up to date. A chapter dealing with pre- and postoperative nutrition and the electrolytes could be advantageously added.

C. O. R.

► WILLIAMS OBSTETRICS - - -

By Nicholson J. Eastman, M.D., Professor of Obstetrics, Johns Hopkins University School of Medicine; Obstetrician-in-Chief to the Johns Hopkins Hospital, Baltimore. Ed. 10. 1,200 pages, with 696 illustrations, some in color. 1950, Appleton-Century-Crofts, Inc., New York. $12.50.

The first six editions of this popular text were written by the late J. Whitridge Williams, the first edition in 1903. The next three editions were prepared by the late Henricus J. Stander and this most recent edition by Nicholson J. Eastman, Professor of Obstetrics, Johns Hopkins University. The text has been extensively rewritten, much new material added and obsolete matter of only historical interest—except that retaining classical interest—has been deleted.

A new first chapter has been introduced to orient the student of obstetrics from the broad perspective of vital statistics, public health and medicine in general. Other new material includes a new and simplified classification of toxemia and revised concepts concerning ovarian and placental hormones, estimation of pelvic size and shape, the forces concerned in labor, analgesia and anesthesia, abortion, clinical aspects of ectopic pregnancy, clinical aspects of placenta previa, treatment of syphilis, management of uterine inertia, rupture of the uterus, postpartum hemorrhage, hemolytic diseases of the newborn and others.

The addition of many new illustrations, a new format designed for easy reading, and a new subject index, in addition to the general excellence of the text, should insure a continuation of the popularity enjoyed by this text since the turn of the century.

M. B. S.

► AN ATLAS OF HUMAN ANATOMY - - -

By Barry J. Anson, Ph.D., Professor of Anatomy, Northwestern University Medical School. 518 pages. 1950, W. B. Saunders Company, Philadelphia & London. $11.50.

Confining the subject matter to drawings demonstrable in actual cadaver prosection, the author presents a noteworthy advance in the field of illustrative anatomy. The volume is designed to assist students in their dissections, but more so to recall forcibly the true aspect of gross anatomy when later confronted with surgical problems.

The tendency in the medical schools partially to sacrifice academic study of gross anatomy necessitates a monograph of this type to replace the actual dissected specimens. It behooves all practitioners to sharpen their clinical judgment on the basis of applied anatomy, and this edition is particularly applicable to the development of such medical acumen.

The sketches are readily delineated and derived from new dissections with unusual artistic skill. They are clear and concise and accompanied by interpretation that leaves no doubt as to the morphologic features. The scope of any volume related to anatomic presentation generally predisposes it to a certain unwieldiness; however, this atlas serves as an immediate reference for all structural considerations.

Divided under seven main headings with superb pictorial content untinted by preconceived notions. this edition will be universally accepted as a great contribution to the study of anatomy.

H. O'P.

Books received will be acknowledged in this department each month. As space permits, books of principal interest to our readers will be reviewed more extensively.

A Text-Book of X-Ray Diagnosis by British Authors in four volumes. Edited by S. Cochrane Shanks, M.D., F.R.C.P., F.F.R., Director, X-ray Diagnostic Department, University College Hospital, London: and Peter Kerley, M.D., F.R.C.P., F.F.R., D.M.R.E., Director, X-ray Department, Westminister Hospital; Radiologist, Royal Chest Hospital, London. Volume 3. 830 pages with 694 illustrations. 1950, W. B. Saunders Company, Philadelphia & London. $18.00.

Progress in Gynecology. Edited by Joe V. Meigs, M.D., Clinical Professor of Gynecology, Harvard Medical School; Chief of Staff of the Vincent Memorial Hospital, the Gynecological Service of the Massachusetts General Hospital; Surgeon, Pondville Hospital; Gynecologist, Palmer Memorial Hospital, and Somers H. Sturgis, M.D., Clinical Associate in Gynecology, Harvard Medical School; Assistant Surgeon, Massachusetts General Hospital, Boston. Volume 2. 821 pages, illustrated. 1950, Grune & Stratton, New York. $9.50.

Therapeutics in Internal Medicine. Edited by Franklin A. Kyser, M.D., M.S., F.A.C.P., Associate in Medicine, Northwestern University Medical School, Chicago; Attending Physician. Evanston Hospital, Evanston, Illinois. 715 pages. 1950, Thomas Nelson & Sons, New York. $12.00.

1950 Year Book of Medicine. Edited by Paul B. Beeson, M.D., J. Burns Amberson, M.D., William B. Castle, M.D., Tinsley R. Harrison, M.D., and George B. Eusterman, M.D. 819 pages, illustrated. 1950, The Year Book Publishers, Inc., Chicago. $5.00.

1950 Year Book of Pediatrics. Edited by Henry G. Poncher, M.D., Professor and Head, Department of Pediatrics, College of Medicine, University of Illinois; with the collaboration of Julius B. Richmond, M.D., Associate Professor, Department of Pediatrics, College of Medicine, University of Illinois. Isaac A. Abt, M.D., Editor Emeritus. 504 pages, illustrated. 1950, The Year Book Publishers, Inc., Chicago. $5.00.

Physical Examination in Health and Disease. By Rudolph H. Kampmeier, A.B., M.D., Associate Professor of Medicine, Vanderbilt University School of Medicine; Visiting Physician to Vanderbilt University Hospital; Chief of the Medical Outpatient Service, Vanderbilt University Hospital, Nashville, Tennessee. 821 pages with 550 illustrations, 1 in color. 1950, F. A. Davis Company, Philadelphia. $8.00.

Medical Entomology; With Special Reference to the Health and Well-Being of Man and Animals. By William B. Herms, Sc.D., Late Professor of Parasitology, Emeritus, University of California; one-time Lecturer in Tropical Medicine, University of California Medical School, San Francisco; late Chairman, Division of Entomology and Parasitology, University of California. Ed. 4. 643 pages, illustrated. 1950, The Macmillan Company, New York. $9.00.

Researches in Binocular Vision. By Kenneth N. Ogle, Ph.D., Section on Biophysics and Biophysical Research; Research Consultant in the Section on Ophthalmology, Mayo Foundation and Mayo Clinic, Rochester, Minnesota. 345 pages, with 182 figures and 26 tables. 1950, W. B. Saunders Company, Philadelphia & London. $7.50.

Progress Volume to accompany Hyman's Integrated Practice of Medicine. An appraisal of latest developments in therapeutics prepared by Harold Thomas Hyman, M.D., to accompany his 4-volume Integrated Practice of Medicine. Contains cross reference to the original 4 volumes and an index system to all 5 volumes. 734 pages. 1950, W. S. Saunders Company, Philadelphia & London. $10.00.

Pediatric X-ray Diagnosis; A Textbook for Students and Practitioners of Pediatrics, Surgery & Radiology. By John Caffey, A.B., M.D., Professor of Clinical Pediatrics, College of Physicians and Surgeons, Columbia University; Attending Pediatrician and Roentgenologist, Babies Hospital and Vanderbilt Clinic, New York City; Consulting Pediatrician, Grasslands Hospital, Westchester County, New York, and New Rochelle Hospital, New Rochelle, New York; Consulting Roentgenologist, Orange Memorial Hospital, Orange, New Jersey; Consultant in Pediatric Roentgenology, The New York Hospital, New York City. Ed. 2. 862 pages, with 1039 figures. 1950, Year Book Publishers, Inc., Chicago. $22.50.

Consultation Service

This special consultation information service is offered as a regular monthly feature of *Postgraduate Medicine*. Subscribers are invited to call on this Service for answers to difficult medical problems from members of our Editorial Board and our Editorial Consultants best qualified to help. Each question will be answered by mail and those of general interest will be published each month. Address all communications to Consultation Service, *Postgraduate Medicine*, 516 Essex Building, Minneapolis 3, Minnesota.

ETIOLOGY OF PRE-ECLAMPSIA

QUESTION: How often in pre-eclampsia is there evidence of anterior pituitary adrenocortical hormone stimulation as evidenced by pronounced eosinopenia, sodium and chloride retention, increased urinary 17-ketosteroids and uric acid excretion. I am thinking of an editorial in the *J.A.M.A.* for August 26, 1950. If ACTH overproduction is felt to be a factor in a certain pre-eclamptic, what drugs (dosage and precautions) could be used to attempt to overcome this condition if we assume that adrenalin oversecretion is the cause?

M.D.—Ontario

ANSWER: New concepts of the etiology of toxemia of the latter months of pregnancy have been advanced for many years. Evidence at present points to some upset in what is normally a complicated metabolic process. In recent time an aberration of the gonadotropic-estrogen-progesterone relationship has received much attention. Many have believed that the problem is much more complex than this, and the adrenal gland has often been mentioned in discussing possible causes. Experience with the administration of ACTH and cortisone probably gives a lead in this direction.

Currently, our knowledge is insufficient to indicate a treatment pattern for pre-eclampsia based on the interrelationship of ACTH and hormones of the adrenal cortex.

TREATMENT OF APLASTIC ANEMIA

QUESTION: I have a patient suffering from aplastic anemia. Liver extract, vitamin B_{12}, various iron preparations have no effect whatever on the course of his condition. At present he is getting three to four transfusions every three or four weeks which will elevate the hemoglobin to 60 per cent and red blood cells to approximately 3,000,000, but in less than two weeks the hemoglobin usually drops to approximately 35 per cent.

I am anxious to know if any new therapy has been developed for this serious condition as my patient is becoming quite discouraged.

M.D.—Ontario

ANSWER: In regard to the patient with aplastic anemia it is very important to know if the diagnosis has been substantiated with bone marrow puncture and study. Is there any known cause of the aplasia of the bone marrow? If not, there isn't much that can be done other than to give transfusions and other supportive therapy.

TOM D. SPIES

PRESENTING COMPLAINT—ATROPHY OF LEG

QUESTION: Could you give any suggestions as to the diagnosis and treatment of a man, 65 years of age, whose only complaint is an atrophy of the left leg (thigh). This patient has noticed weakness in his left leg for the past few months, but only recently observed the difference in size. He had a prostatectomy four months ago. Outside of that, his past history, by systems and physical examination is normal.

M.D.—Wisconsin

ANSWER: Some type of neurologic lesion most likely is present. A protruded intervertebral disk, a tumor of the cord or even a neuroma in one of the peripheral nerves, such as the femoral nerve, should all be ruled out. Less likely would be a degenerative or inflammatory disease of the cord or nerve roots.

Since the patient is at an age when malignant disease is relatively common, primary or metastatic malignant growths, with nerve root involvement, must be considered, especially in view of the prostatectomy four months previously. One should therefore proceed along these lines with a thorough neurologic examination and consultation with an orthopedist and a neurosurgeon. Myelographic studies made with the aid of contrast media, may be necessary. Roentgenologic examination of the skeletal system is, of course, essential.

Treatment naturally depends on what is found after these diagnostic measures have been done.

ON THE USE OF CORTISONE

QUESTION: What laboratory controls should be set up in a hospital for the use of cortisone?

What are the present indications for its use?

Would cortisone be contraindicated in a diabetic with severe burns—or say acute rheumatic fever?

Would it be contraindicated in a man with congestive heart failure (e.g. a hypertension basis) with severe iritis?

M.D.—Windsor, Ontario

ANSWER: All things considered, it would be best to refer to the syllabus on cortisone put out by Merck & Co., Inc. These instruction sheets should be available at the hospital where cortisone is available. This syllabus also can be had from Merck & Co., Inc., Rahway, New Jersey. It should answer the questions regarding what laboratory control

should be set up in a hospital and also the indications for cortisone.

The answers to the last question are dealt with to some extent in the afore-mentioned instruction sheets. However, it might be worth while to amplify a reply regarding the use of cortisone in either severe burns or acute rheumatic fever in a patient who has diabetes. Whether or not cortisone should be used ought to depend on the seriousness of the primary disease. Even in mild diabetes, cortisone can be used if indications are sufficient to warrant its use, provided the attending physician is prepared to handle the aggravation in the diabetes which may occur during the time cortisone is given. The patient will require more insulin, and his condition must be followed carefully.

In the case of congestive heart failure due to hypertension in a patient with severe iritis, it will be best to treat the iritis conservatively. Attempts could be made to treat the eye with cortisone used locally in the eye, although special solutions should be obtained for this. I am not in favor of using cortisone by injection for a patient who has heart failure due to hypertension unless such a step seems to be extremely urgent, because of the possible aggravation of congestive heart failure due to retention of fluids. It might be possible to proceed satisfactorily with the use of cortisone if a low-sodium diet were prescribed for the patient.

BILATERAL SALPINGECTOMY

QUESTION: I am interested in obtaining all the available literature on reparative surgery following bilateral salpingectomy. It has come to my attention that there is a new method of opening the base of the Fallopian tube either with the use of plastic or a fibrin tube.

Any information that you can obtain for me or of which you can tell me the source will be very much appreciated.

M.D.—California

ANSWER: The answer to this question cannot be limited to the restrictions of the question. Bilateral salpingectomy would confine the discussion of reparative surgery for relief of sterility strictly to the subject of ovarian implantation into the wall of the uterus (Estes, W. L.: Ann. Surg. 82:475, 1925; and Estes, W. L., Jr., and Heitmeyer, P. L.: Am. J. Surg. 24:563, 1934).

All other reparative surgery including the use of tubes or cannulas requires as a prerequisite enough of a patulous Fallopian tube or tubes to permit their implantation through a new opening into the uterine cavity. Thus such surgery is not applicable when bilateral salpingectomy has been done.

The entire subject of plastic surgery for relief of absolute sterility caused by tubal disease or defects has been covered in the monograph on Sterility and Impaired Fertility, by Lane-Roberts and his associates (Ed. 2, London, 1948, Hamish Hamilton Medical Books) and in this writer's book, Management of Obstetric Difficulties (Ed. 4, St. Louis, 1950, C. V. Mosby Company). Much of the pioneer work was done by Strassman, by Cullen, by Watkins, and by Holden and Sovak. The original references can be found in the bibliographies of the two books mentioned above.

An outstanding appraisal of the effectiveness and of the results of such operations is that by J. P. Greenhill (Am. J. Obst. & Gynec. 33:39, 1937). His opinion about them is even more pessimistic than that of B. Solomons (Surg., Gynec. & Obst. 60:352, 1935).

Impressed by their views, B. B. Weinstein (South. Surgeon 14:556, 1946) and Vincente D'Ingianni (South. M. J. 41:575, 1948) undertook to devise measures for maintaining the patency of Fallopian tubes after their implantation.

In the first place the condition to which the operation of tubal implantation lends itself is solely that in which there is obstruction of the canal of the Fallopian tubes at or near to their interstitial portion. Their outer two-thirds must be patent. Parenthetically, the tubes obstructed at the fimbriated ends are subjected, for reparative surgery, only to the circumcision or "cuff" operation of F. C. Holden and F. W. Sovak (Am. J. Obst. & Gynec. 24:684, 1932).

In the implantation operation the obstructed portion is freed, resected and drawn into the cavity of the uterus by traction sutures through an orifice reamed, or cut by simple incision, through the upper wall of the uterus into its cavity.

The contributions to this technic by Weinstein and by D'Ingianni consisted in efforts to prevent secondary or postoperative obstruction in the implanted portion of the tube. Weinstein drew the tube over a projecting cannula or tube of glucose which absorbed in about ten days.

D'Ingianni implants the tube over a metal cannula attached to a stainless steel wire previously passed down through the cervix into the vagina, so that it can be left in place several weeks and then be withdrawn by simple traction on the wire from below. He has reported a considerable degree of success in a necessarily limited number of cases, namely three pregnancies and living babies in 17 such operations or an incidence of 20 per cent.

It is likely that this is the work to which the correspondent refers when he asks concerning the use of plastic or fibrin tubes, although it is possible that these tubes mentioned by him have been substituted as a modification of the other technics cited above. If so, it will be necessary to ask anyone knowing of this work to furnish the bibliographic reference, as it is not familiar to this writer.

PAUL TITUS

New Drugs *and* Instruments

Information published in this department has been supplied by the manufacturers of the products described.

PARBROM

PURPOSE: Treatment of premenstrual tension and motion sickness.

COMPOSITION: N,N-dimethyl-N′-pyridyl-N′-p-methoxybenzylethylenediamine-8-bromtheophyllinate.

DOSAGE AND ADMINISTRATION: In premenstrual tension: 1 tablet three times a day, beginning three to five days before expected menstruation, or beginning when symptoms are expected. Should side effects such as drowsiness or dizziness appear, reduce the dosage. Parbrom medication should be discontinued at the first appearance of flow. Dosage should be limited to a total of 3 tablets per day for a period not exceeding seven days in duration. In motion sickness: 1 to 2 tablets thirty minutes to an hour before beginning of the journey, and 1 to 2 tablets, if needed, every three or four hours. Dosage should be limited to a total of 6 tablets per day for a period not exceeding seven days.

CAUTION: In some individual cases, there may be drowsiness or dizziness, so that on the days Parbrom is taken, the patient should abstain from driving an automobile or operating dangerous machinery. Parbrom is to be dispensed only by or on the prescription of a physician.

HOW SUPPLIED: 50 mg. tablets, bottles of 100.

PRODUCER: The Central Pharmacal Co., Seymour, Ind.

KUTROL

PURPOSE: Treatment of crateriform duodenal ulcers.

COMPOSITION: An extract of pregnancy urine, also known as anthelone, a buff-colored amorphous powder free from unpleasant odor or taste.

DOSAGE AND ADMINISTRATION: Usual dosage is 2 Kapseals 4 times daily.

HOW SUPPLIED: Kutrol Kapseals, 75 mg., bottles of 100.

PRODUCER: Parke, Davis & Co., Detroit, Mich.

OPTILETS

PURPOSE: Therapeutic formula vitamin tablets.

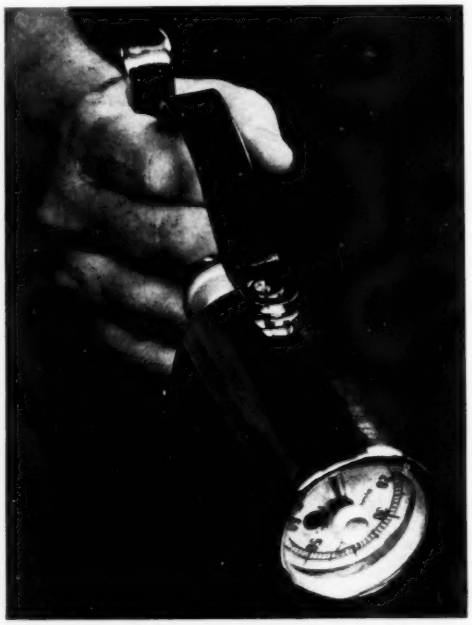
COMPOSITION: Each small, orange, ovoid tablet (sugar-coated) contains:

Vitamin A (synthetic)	25,000 U.S.P. units
Vitamin D (viosterol)	1,000 U.S.P. units
Thiamine mononitrate	10 mg.
Riboflavin	5 mg.
Nicotinamide	150 mg.
Vitamin B_{12} (as vitamin B_{12} concentrate)	1.5 micrograms
Ascorbic acid	150 mg.

DOSAGE AND ADMINISTRATION: One tablet daily for prophylaxis; physician to determine therapeutic doses.

HOW SUPPLIED: Bottles of 50, 100 and 1,000 tablets.

PRODUCER: Abbott Laboratories, North Chicago, Ill.



MYOMETER GRIP-TESTER

PURPOSE: Newman myometer for muscle testing with removable Grip-Tester frame.

DESCRIPTION: Instrument can be used for grip-testing and testing of many other muscles throughout the body. For grip-testing, the hand to be tested is allowed to grip the specially designed finger and palm rest and the peak of the effort is registered in the dial gauge. After the dial reading has been noted, the gauge hand is manually reset to zero.

HOW SUPPLIED: Zero to sixty pound Myometer Instrument complete with Myometer Grip-Tester in a case with Equalizing Disc. For those who have the Myometer Instrument, the Grip-Tester frame may be purchased separately.

PRODUCER: Burton Mfg. Co., Los Angeles, Calif.

NORMOCYTIN* Vitamin B_{12b} and B_{12} with FOLVITE* Folic Acid TABLETS

PURPOSE: Treatment of the megaloblastic anemias.

COMPOSITION: Each tablet contains 30 micrograms of vitamin B_{12b} and B_{12} with 1.67 mg. of folic acid.

HOW SUPPLIED: Bottles of 100 tablets.

PRODUCER: Lederle Laboratories Division, American Cyanamid Company, Pearl River, N. Y.

*Trademarks.

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UNIVERSAL MONOCHROMATOR

PURPOSE: Light source in the ultraviolet, visible and infrared portions of the spectrum.

DESCRIPTION: Among its features are: totally reflecting optics, permitting focusing in the visible for infrared and ultraviolet use; range of 0.18 to 40 microns (with suitable prisms); dimensions 14 by 14 by 9 inches; focal length 270 mm.; effective aperture f/4.5. A wide variety of accessories such as special prisms, various types of liquid and gas absorption cells, and the like are available.

PRODUCER: The Perkin-Elmer Corp., Glenbrook, Conn.

AQUACILLIN-A.S.

PURPOSE: Aqueous suspension of procaine penicillin G for intramuscular injection.

DESCRIPTION: Ready for instant use; stable—may be stored for one year at room temperature.

DOSAGE AND ADMINISTRATION: One cubic centimeter (300,000 units) provides therapeutic levels for at least 24 hours; 1 cc. every 24 hours is ample for most infections. For overwhelming infections 1 cc. injections every 12 hours or 2 cc. injections daily.

HOW SUPPLIED: 1 cc. vial—300,000 units; 5 cc. vials—1,500,000 units; 10 cc. vials—3,000,000 units; vial with disposable cartridge syringe (300,000 units).

PRODUCER: Schenley Laboratories, Inc., New York, N. Y.

TRI-SULFAMETH

PURPOSE: Oral sulfonamide therapy.

COMPOSITION: Each 5 cc. of syrup or each tablet supplies:

Sulfadiazine	0.165 gm. (2.5 gr.)
Sulfamerazine	0.165 gm. (2.5 gr.)
Sulfamethazine	0.165 gm. (2.5 gr.)
Sodium citrate (not contained in tablets)	0.5 gm. (7.7 gr.)

INDICATIONS FOR USE: In all infections due to sulfonamide-susceptible organisms.

DOSAGE AND ADMINISTRATION: Infants and children, initial dose of 0.1 gm. per kilogram of body weight, followed by one-fourth the initial dose every 6 hours. Adults, initial dose of 3 to 4 gm. followed by 1 gm. every 6 to 8 hours until temperature has remained normal for 48 to 72 hours. In very severe infections, dosage may be increased by 50 per cent.

HOW SUPPLIED: Syrup, bottles of 4 oz., 16 oz., and 1 gallon. Tablets, bottles of 50, 100, 500, and 1,000.

PRODUCER: Casimir Funk, Inc., New York, N. Y.

MICROPELLETS® ORETON-F®

PURPOSE: Aqueous suspension of testosterone.

DOSAGE AND ADMINISTRATION: Administered by intramuscular injection. A 21-gauge, 1½ inch needle is recommended. After withdrawal of needle, brief massage over the site of injection serves to distribute and aid absorption of the hormone. In males: 25 mg. 3 to 5 times weekly in hypogonadism; 3 times weekly in the male climacteric; 3 to 4 times weekly in impotence, with reductions of dosage in each case to maintenance levels. In females: 100 mg. 3 times weekly as initial therapy in advanced breast carcinoma; 25 mg. every other day for 3 or 4 doses in functional uterine bleeding; 10 mg. daily for last 10 days of cycle in dysmenorrhea; 25 mg. twice daily for 2 days in inhibition of lactation; 25 mg. after delivery and repeated 8 hours later, if desired, for postpartum after-pains.

HOW SUPPLIED: Multiple dose vials of 10 cc., containing 25 mg. or 50 mg. per cubic centimeter. Boxes of 1 and 6 vials.

PRODUCER: Schering Corp., Bloomfield, N. J.

OXSORBIL CAPSULES

PURPOSE: Aid drainage of bile ducts and enhance fat emulsification.

COMPOSITION: Each capsule contains:

Dehydrocholic acid	½ gr.
Desoxycholic acid	½ gr.
Extract of ox bile, U.S.P.	1 gr.
Sorbitan monooleate polyoxyethylene derivative	2½ gr.
Oleic acid, U.S.P.	2¾ gr.

INDICATIONS FOR USE: In chronic cholecystitis, noncalculous cholangitis, postcholecystectomy syndrome, biliary dyskinesia, biliary stasis in the absence of total obstruction.

CAUTIONS: Contraindicated in severe hepatitis, acute yellow atrophy of liver, complete mechanical common duct obstruction. May be contraindicated during mineral oil therapy.

DOSAGE AND ADMINISTRATION: Suggested dosage is 1 to 2 capsules 3 times a day or as directed by physician.

HOW SUPPLIED: Bottles of 100 gelatin capsules.

PRODUCER: Ives-Cameron Co., Inc., New York, N. Y.

FENOXYDYNE COMPOUND

PURPOSE: Treatment of the common cold.

COMPOSITION: Each tablet contains fenoxydyne citrate 25 mg., acetophenetidin 320 mg., caffeine 32 mg.

DOSAGE AND ADMINISTRATION: One or two tablets every three or four hours for at least forty-eight hours, taken as soon as possible after onset of symptoms. For children 6 to 12 years of age, half the adult dose.

HOW SUPPLIED: Bottles of 25, 100, 500, and 1,000 tablets.

PRODUCER: George A. Breon & Co., Kansas City, Mo.

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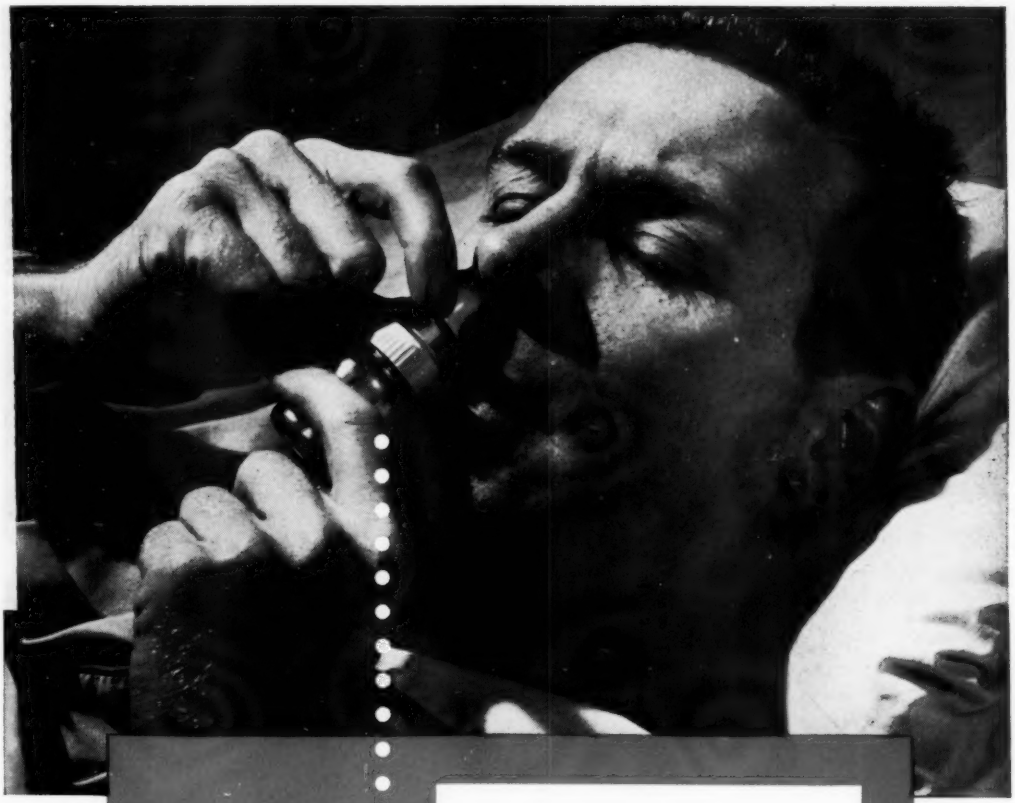

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1. Filler, W.: J. A. M. A., 143: 1235 (Aug. 5,) 1950

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